BRONCHIOGENIC CARCINOMA AND ADENOMA

With a Chapter on

MEDIASTINAL TUMORS

B. M. FRIED, M.D.

Associate Attending Physician
Montefiore Hospital for Chronic Diseases, New York



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TO MY WIFE

Il n'y a pas de problèmes insolubles, il n'y a que des questions mal posées

Claude Bernard

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Chapter I

INCIDENCE

Statistical Increase. The few cases of bronchiogenic cancer reported during the past century were regarded at the time as unique findings. Today, in the gallery of malignant tumors, cancer originating in the lung is no longer considered a rarity. Patients with this disease are observed daily and the literature abounds in reports.

The incidence and the alleged increase of the disease is still a matter for discussion. According to available figures the relationship between pulmonary cancer and cancer of other organs rose within three decades, 1900-1930, from 1.5 per cent to 10 per cent. It is also to be noticed that from 1910 to 1920 it occurred in about 4.5 per cent, while in the following decade, 1920-1930, its incidence went up to about 7 per cent.

The fact that bronchiogenic cancer was not observed or not recorded in the past while at present it is diagnosed frequently has impressed observers who have declared that a new disease made its appearance, probably a result of our peculiar modes of living — another "gift" of modern civilization.

The decades following World War I were remarkable by the compilation of numerous statistical data interpreted by some as showing that it is incontestably a "new disease" mounting in frequency under our very eyes. Others challenged the view by stating that the increase is more apparent than real.

In order to study the occurrence of bronchiogenic carcinoma in the Pacific Northwest, Menne and Anderson sent out a questionnaire to the members of the Pacific Northwest Society of Pathologists requesting figures showing the incidence of cancer observed post mortem. The returns revealed that from 1920 to 1940 five hundred and seventeen, or 1.52 per cent, of cases of bronchiogenic cancers were found in 33,945 autopsies (table 1).

What impressed Menne and Anderson most was the fact that during the last two periods, namely, from 1931 to 1935 and from 1936 to 1940, there was an "astonishing and sharp" rise (tables 2 and 3). The authors believed that the higher percentage at the Vancouver General Hospital was probably due to less generalization in the performance of autopsies. They arrived at the conclusion that there was both a relative and absolute increase of bronchiogenic carcinoma.

Ochsner and DeBakey found that the incidence of pulmonary carcinoma in the necropsies performed at the Charity Hospital in New Orleans had multiplied in seven years approximately five times. In 1931, of 635 autop

sies there were 3, or 0 47 per cent of cases, while in 1938, of 826 autopsies, there were 17, or 2 per cent "It is evident," they asserted, "that pulmonary carcinoma is absolutely increasing "

The ratio of pulmonary carcinoma to all carcinoma at Yale University Medical School rose from 7 4 per cent from 1917 to 1927 to 11 per cent from 1928 to 1937 The opinion of Rosahn, who analyzed the material, was that the increase was real and absolute

TABLE 1

Incidence of Bronchiogenic Cancer in the Pacific Northwest

YEARS	NUMBER OF CASES
1920–1925	3
1926–1930	63
1931–1935	201
1936–1940	407

TABLE 2

Incidence of Bronchiogenic Carcinoma at the University of Oregon

YEARS	AUTOPSIES	LUNG CANCER	PERCENTAGE TO ALL CANCERS
1928–1933	3129	23	0 73
1934–1937	2820	26	0 92
1938–1940	2022	34	1 68

TABLE 3

Incidence of Bronchiogenic Carcinoma at the Vancouver General Hospital

YEARS	AUTOPSIES	LUNG CANCER	PERCENTAGE TO ALL CANCERS
1928–1933	2111	35	1 65
1934–1937	2206	40	1 81
1938–1940	2244	56	2 49

The incidence of bronchiogenic carcinoma at the Boston City Hospital is shown in table 4

Olson, who reported the figures collected in this table, stated "There was an abrupt increase, probably due to tremendous expansion of the Boston City Hospital in recent years, increased interest in pulmonary surgery, many patients were allowed to remain in the hospital, whereas formerly they were sent to institutions for incurables " The figures for 1930–1934 which showed an absolute increase were attributed by Olson to a "selective

phenomenon." It is of interest that from the same material Rosahn drew opposite conclusions.

Jaffé analyzed 6800 autopsies performed at the Cook County Hospital, Chicago, where primary carcinoma of the lung comprised 11.47 per cent of all cancers. "In 1921," he wrote, "I published from a different part of the world (Vienna, Austria), statistics which were based upon 4500 autopsies performed between 1915 and 1918. In these statistics, the incidence of pulmonary carcinoma was 10.73 per cent. I am inclined to believe with others that the increase in frequency of primary carcinoma of the lung is more apparent than real."

TABLE 4

Bronchiogenic Cancer at the Boston City Hospital

YEARS	NUMBER OF ADULT AUTOPSIES	CARCINOMAS		PRIMARY LUNG CANCER		
		Total	Autopsies	Total	Autopsies	All carcinomas
1900–1904	931	57	6.12	2	0.21	3.50
1905–1909	865	52	6.01	4	0.46	7.69
1910–1914	438	34	7.76	2	0.45	5.88
1915–1919	526	45	8.55	2	0.38	4.44
1920–1924	957	99	10.34	7	0.73	7.07
1925–1929	1532	182	11.87	14	0.91	7.69
1930–1934	2624	293	11.16	38	1.44	12.96
Total	7873	762	9.67	69	0.87	9.06

The incidence of primary carcinoma of the lung at the Johns Hopkins Hospital is given in table 5. "If we judge from hospital autopsy statistics," commented MacCallum, "a slight but perceptible increase in the cancers of the lung had occurred. Such figures must, however, be received with great caution." ... "Statistics must be examined very critically because so many factors may vitiate the conclusion, and in endeavoring to estimate the results of the study of 10,000 autopsies in the Johns Hopkins Hospital we have found it almost impossible to give precise weight to each of these objections."

Steiner reports that in the forty years from 1902 to 1941 inclusive, primary carcinoma of the lung was noted in 126 of 5,515 necropsies performed at the University of Chicago. The incidence was 2.3 per cent of all necropsies, 7.6 per cent of all malignant tumors and 10.3 per cent of all tumors diagnosed as carcinoma. It was fifth in frequency among all types of tumor and third among types of carcinoma. The incidence of carcinoma of the lung expressed in terms of percentage of all tumors showed a slight increase in males but not in females. The increase was less than that shown

for two types of tumors used as controls, namely carcinoma of the colon and intracranial tumors but greater than that for two other control types carcinoma of the pancreas and carcinoma of the stomach Corrections were made for changes in the annual number of necropsies, in the sex ratio of all necropsies in the percentage of neoplasms in all necropsies and in the average age of the necropsy population The only known variable not subjected to correction a change in the nature of patients admitted to the hos-

TABLE 5

Bronchiogenic Carcinoma at the Johns Hopkins Hospital

YEARS	AUTOPSIES	CARCINOMAS		PERCENTAGE OF ALL CARCINOMAS
		All	Lung	
1890–1895	606	72	0	0
1895–1900	856	73	1	1.39
1900–1905	988	84	0	0
1905–1910	868	82	4	5.00
1910–1915	943	75	2	2.60
1915–1920	1848	95	3	3.15
1920–1925	2315	113	7	5.20
1925–1930	2830	186	13	7.00

TABLE 6

Bronchiogenic Cancer in Great Britain

YEARS	ADMISSIONS	LUNG CANCERS AT AUTOPSY	PER CENT CE IN ADMISSION
1894–1898	315,059	173	0.055
1899–1903	374,207	180	0.048
1904–1908	420,595	234	0.055
1909–1913	509,193	331	0.065
1914–1918	625,833	257	0.041
1919–1923	671,846	386	0.057
1924–1928	786,912	552	0.070

pitals could easily account for the slight increase in carcinoma of the lung He believed that there has been a slight apparent but no real increase in primary carcinoma of the lung

Combined figures of seven hospitals of Great Britain (London, the Provinces Scotland) for the years 1894 to 1928 (table 6) inclusive showing the incidence of bronchiogenic cancer have been reported by Passey and McD Holmes who arrived at the following conclusions The evidence afforded does not support the widely held view that the incidence of intrathoracic neoplasia is appreciably on the increase especially if due allowance

be made for the altered conditions of today in comparison with those of the pre-war (World War I) period

Klotz from a detailed review of the available literature, concluded "Most of the authors consider the increase purely apparent"

Of 6 500 autopsies performed at the Montefiore Hospital New York, 2 0((or 31 8 per cent showed cancer Of these, three hundred and nineteen or 15 44 per cent arose in the lungs The relationship of bronchiogenic cancer to cancer of other organs is shown in chart 1

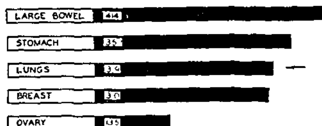


CHART 1 Cancer of the bronchus and cancer of other organs in 6,500 necropsies

TABLE 7

ORGAN	CARCINOMAS	PERCENTAGE TO ALL POST MORTEMS	PERCENTAGE TO ALL CARCINOMAS
Large bowel	414	6 7	20 00
Stomach	352	5 4	17 00
Lung	319	4 09	15 44

From chart 1 it may be seen that at the Montefiore Hospital carcinoma of the large bowel occupies the first place 414 cases carcinoma of the stomach the second 352 cases and carcinoma of the lung the third 319 cases The percentage relationship of these cancers is demonstrated in table 7

It will be shown later that in the male cancer of the lung occurs almost as frequently as cancer of the stomach both at the head of the list

At the Montefiore Hospital the steady rise in the number of cases of bronchiogenic cancer went parallel with the increase of the number of admissions deaths and necropsies

Statistics Disraeli is credited with the statement that statistics are a dismal science It is complex as well as dismal Conclusions drawn from this science to be convincing must fulfill a number of criteria such as the growth and economic status of the population, the state of public health (High crude cancer deaths is evidence of a good state of public health H G Wells) standards of medical education hospitalization fa

cilities In none of the reported studies were these prerequisites considered As a rule statisticians dealt with crude figures obtained from clinical and/or post mortem records It is striking, indeed that the *Quarterly Cumulative Index* registered but one reference on cancer of the lung in 1920, while in 1931 it recorded 41 However, it is well to point out that in 1920 the European continent just emerged from the ravages of the World War when civilian hospitals were depleted of physicians and clinical research was virtually at a standstill

It is argued that if cancer of the lung were prevalent in the past it would have surely been noted by pathologists, particularly of the calibre of Rokitanski or Virchow In fact writers referred to Morgagni who allegedly identified primary carcinoma of the lung However, this statement is not based on fact To the day of Laennec no authentic case of this disease could be found on record The horse sense" with which older physicians were allegedly endowed was of no avail in matters where an anatomo pathologic background is essential and where accessory means of diagnosis are necessary Laennec pointed out that physicians throughout the ages usually ceased visiting their incurable (chronic) patients He found that Hippocrates left scant notes on chronic diseases Le pétit nombre de connaissance qu il nous a transmise sur les maladies organiques lentes vient peut etre de ce qu il cessai de visiter les malades dans les affections confirmées de ce genre (The meagre information which Hippocrates left on chronic organic diseases was probably due to the fact that he usually discontinued visiting patients when he became aware of the chronicity of their affection) Chronic and incurable patients were relegated to monasteries mostly abandoned like the wounded on the battlefield

Even more recent founders of medical doctrines " like Boerhave Corvisart, Bayle and others had no understanding of cancer of the lung Corvisart wrote Je ne sache pas qu'on ait jamais observé un des organes pulmonaires dans un état strictement scirreux ou degeneré en cancer (I am not aware of the fact that a lung has ever been found in a strictly scirrous condition or that it had been degenerated into cancer)

To Bayle cancer of the lung was *une sixieme sorte de phthisie* —a sixth variety of phthisis Bayle is universally quoted as the first author who recorded in 1810 a case of pulmonary cancer combined with tuberculosis of the lung How this case was misinterpreted by him will be told in Chapter III The description of an allegedly primary carcinoma of the lung by Laennec stands no modern test

Pathologic Anatomy in the 19th Century Almost to the end of the nineteenth century pathologic anatomy was in a state of confusion, although isolated contributions were highly meritorious The histologic aspect of tumors their histogenesis and mode of spreading were vaguely understood

In the chapter on carcinoma of the lung, in Ziemssen's *Handbuch Der Speziellen Pathologie und Therapie* (vol 5, p 416, 1874), appeared the following

"Without doubt the tumor (of the lung) here originated in the interlobular connective tissue, compressing the lobules and the alveoli at times penetrating into them, without however, leading to neoplastic transformation of the respiratory epithelial cells"

The noted physician Maurice Raynaud wrote in 1874

"In the present state of science one no longer bases an anatomic diagnosis of cancer on the cellular morphology of which the tumor is made up for it is never constant and may vary infinitely Accordingly one no longer admits the expression '*cancer cells*' but *cancerous tissues*' which consists on the one hand, of an alveolar fibrous stroma and on the other hand of cells lodged in alveoli"

Virchow, in 1884 stated

There are tumors such as gliomas which originate through hyperplasia of embryonic tissue I also reported observations where elements of epithelial character originated from connective tissue by way of metaplasia I for my part am convinced that epithelial tumors may originate from connective tissue by way of metaplasia As far as pathologic anatomic observations go fat cells serve as matrices for epithelial cells occurring partly through metaplasia and partly through proliferation

Virchow like others considered Gaucher's splenomegaly an epithelioma of the spleen

Pathologists were influenced by the statement made by Virchow that organs which are frequently the seat of a metastatic involvement by malignant tumors are rarely the seat of a primary new growth This erroneous statement was repeated by Lubarsch in 1895 who cited the lungs as a case in point Since the lungs are the convergent point of the body malignant cells which happen to invade the blood stream invariably reach them forming secondary nodules or masses the latter not infrequently overshadowing the primary growth Moreover the failure of the pathologist to demonstrate grossly a secondary involvement of the lungs by tumor is no longer regarded as conclusive proof of the absence of metastatic tumor in these organs Indeed it was shown that microscopically minute metastases can *almost always be detected in the lung The foregoing has led to the un*founded statement that whenever in the presence of a tumor anywhere in the body tumor is also disclosed in the lungs the lesion in the latter ought to be considered as secondary

Pathologists almost to the end of the past century groped blindly they

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is no longer contested The point at issue is Whether the increase is real or only apparent

The statistical incidence of cancer in general is compiled from observations made by surgical exploration from clinical reports and from post mortem examinations The reliability of cancer statistics has been the subject of numerous controversial investigations

The value of figures of older observers culled from clinical diagnoses of inaccessible (internal) cancers was contested because of the fact that the margin of error in the clinical diagnoses of inaccessible cancers was wide Thus Lubarsch (1924) by investigating the cancer statistics of the German Republic for the years 1920 and 1921, arrived at the conclusion that the errors in diagnoses in the clinical material were so significant (32 44 per cent) that cancer statistics pertaining to incidence and localization of the tumor can have little value Likewise Wells (1923 and 1927) related that in a total of 578 cases of cancer at the Cook County Hospital in Chicago there were 211 incorrect diagnoses—a diagnostic error of 32 5 per cent Such a high ratio of incorrect diagnosis in a great hospital ' said Wells might seem to be evidence of something wrong with the hospital, but we find that other institutions dealing with a similar class of cases in which most of the cancers coming to necropsy are of the internal organs, exhibit not dissimilar figures He quoted Bashford Reichelmann Berenczy and Wolf and Bilz who in London Berlin Budapest and Jena respectively, reached nearly the same conclusions Wilcox whose investigations were published in 1917 and Peller who reported his studies on the incidence of cancer in 1925 are in accord with the ideas of Lubarsch and Wells

The increase in cancer registered in recent years concerned visceral organs while cancer of external organs (accessible and easily diagnosed) showed no rise It is of importance to stress that the statistical increase in cancer was noted in men only while the figures of cancer in women remained virtually unchanged This was due to the fact that cancer in man is essentially visceral (stomach lung) while in woman it is chiefly external (breast, cervix)

Degenerative Diseases It is significant that with the alleged increase in the occurrence of bronchiogenic cancer there was also a rise in the incidence of so-called degenerative diseases Eggers for instance, found that from 1900 to 1924 inclusive the mortality incidence from cancer and from degenerative diseases showed a regular and even increase He noted that cancer and the combined death rate from the usual diseases of advanced age showed an almost proportionate rate of increase for the twenty five year period

Of interest is the observation that deaths due to diseases of the heart and also to arteriosclerosis has markedly increased in the past two decades

understood vaguely the mode of origin, of spread, and even the morphologic aspects of malignant neoplastic diseases The Schneeberger cancer of the lung was identified by Carl Weigert as a lymphosarcoma, while the Joachymstal cancer (see Chapter III) was until 1929 diagnosed as tuberculosis

Adenoma of the bronchus possessing well defined pathologic characteristics was discovered in recent years and tuberculosis of the larger bronchi encountered in about 30 per cent of patients with pulmonary tuberculosis was recorded for the first time about fifteen years ago

Diagnostic Methods in the 19th Century The clinician of the 19th century was not equipped with accessory methods of diagnosis of chronic pulmonary diseases The tubercle bacillus, which is in reality the single criterion in making the diagnosis of pulmonary tuberculosis certain, was discovered in 1882 The roentgen rays as an effective aid in the diagnosis of intrathoracic diseases have been applied successfully in the clinic since the beginning of this century Bronchoscopy and the use of iodized oil are of still more recent origin Finally, surgical exploration in obscure and doubtful cases as practiced in the diagnosis of other visceral organs had not been applied to intrathoracic pathologic conditions, since the lungs had been considered a *noli me tangere* from the surgical standpoint For these reasons neoplastic diseases of the lungs were not identified *intra vitam*

Medicine Revolutionized The eighteen hundred eighties were notable for events that revolutionized medicine

1 The method of Lister inaugurated a new era in surgery opening new vistas in the study of visceral malignant diseases in vivo

2 The discovery of the tubercle bacillus by Koch revealed among other things that chronic cough, hemoptysis and wasting may be caused by diseases other than tuberculosis

3 The doctrine of Metchnikoff (1884) on mesenchymal reactions and inflammation heralded a new era in pathology, under the influence of this teaching, pathologists began to discriminate intelligently between inflammatory and neoplastic processes

4 The discovery of the X rays by Roentgen (1896) enabled clinicians to perform an autopsy in vivo"

Indeed, discussions on the pathologic aspect of bronchiogenic cancer made their appearance in the literature soon after the discoveries of Koch and Metchnikoff, and clinical reports on the disease began to appear following the introduction of the Roentgen rays Passler, in 1896, collected from the literature only 96 cases of pulmonary cancer, while Adler, in 1912, found 370 He stated ' The failure of recognition of cancer of the lung has for a long time perpetrated the dogma of its rarity "

The Issue That primary carcinoma of the lungs is of frequent occurrence

while deaths from diabetes has decreased considerably 'Prior to 1914 wrote Joslin deaths from coma and diabetes reached 61 per cent but since August 1922 have fallen to 10 per cent Coincidentally, deaths from arteriosclerosis have advanced from 15 to 47 per cent Joslin attributed this to prolongation of the life of the diabetics who with the former methods of treatment would have died long before their arteries had become hardened Joslin further related that the average age at the death of 339 patients (Joslin s) in the Naunyn period (1898–1914) was 44 8 years the average age at death of the 607 fatal cases in the present Banting period (since 1920) was 54 2 years and for the last year s 60 fatal cases the average was 59 years Similarly a large part of the population free from tuberculosis as a result of modern hygienic measures has reached a more advanced age only to become the prey to an epithelial malignant disease The morbidity from cancer is in direct proportion to the state of public health

Longevity That the average length of life has considerably increased and a greater proportion of the population reach an advanced age is universally accepted It is known for instance that for centuries before and after the time of King Tut Ank Amen down to the discovery of America the average length of life was eighteen years at the time of the French Revolution it had increased to thirty three years at the time of the Civil War it had advanced to approximately forty five years at present it is over sixty In 1940 the average span of life in the United States was 63 77 years according to tables prepared in the Statistical Bureau of the Metropolitan Life Insurance Company At the age of 19 one has as many years of life before him as the newborn baby in 1900 Fifteen to twenty years have been added during the last three or four decades This is of particular importance in connection with the cancer age

The paucity of knowledge in the past century concerning cancer particularly cancer of the lung invalidates the statement that this disease is of recent origin

Author s View The author is of the opinion that the more frequent occurrence of this disease today as compared with the past can be explained on the basis of the following factors

1 Progress in medicine in the past five decades resulting in improved methods of diagnosis

2 Progress in public health *resulting in increased longevity (more people* reach the cancer age')

3 Vastly developed means of hospitalization

4 Rise in the social and economic levels leading to more people *seeking* medical advice

5 Increased attention to the disease

The increase, therefore is in all likelihood more apparent than real

Sex

Bronchiogenic cancer is more prevalent in the male (fig 1) The incidence of the disease in the two sexes respectively, is shown in table 8

In a review of 8 575 cases from the available literature, Ochsner and DeBakey found 78 9 per cent males and 21 1 per cent females



FIG 1 Sex incidence of bronchiogenic carcinoma

TABLE 8
Sex Incidence of Bronchiogenic Carcinoma

AUTHOR	NUMBER OF CASES	MALES	FEMALES
		per cent	*per cent*
Craver	175	90 30	9 70
Dick	121	82 60	17 40
Fried	319	78 37	21 63
Halpert	135	91 10	9 90
Moersch and Tinney	448	82 60	17 40
Moses	287	70 00	30 00
Palazzio and Mazzei	100	90 00	10 00
Sheik	138	84 00	16 00
Steiner	126	79 37	20 63
Tripoli and Holland	195	80 70	19 30
Total	2047	82 90	17 10

The relationship between bronchiogenic cancer and other cancers (with the exception of cancer of the cervix which is rarely encountered at the Montefiore Hospital) is given in charts 2 and 3

The peculiar selectivity of bronchiogenic cancer for the male has not been adequately explained Some authorities incriminated smoking of cigarettes This explanation though attractive for its simplicity, is hardly plausible

It is to be noted that although there exists a difference in the cancerization of the two sexes as to organ, there is but a slight difference in the *total* morbidity from cancer between men and women However, women are affected by cancer at an earlier age period than men While in men cancer of the lung and of the stomach reaches its peak in the second half of the sixth decade of life (55 to 59), in women the highest incidence of mammary

cervical and ovarian cancers is in the first half of the fifth decade (40 to 44), i e , ten to fifteen years earlier The prevalence of pulmonary cancer in man may possibly be due to the fact that in the female cancer of the genital organs, which occurs with greater frequency at an earlier age, "protects" them against the subsequent development of carcinoma of the respiratory organs either by causing death of the patient before the pulmonary neoplasm has had time to develop, or (in case of survival) by creating a virtual "immunity" or resistance to the development of a new cancer

In this connection the following is of interest· There exists a discrepancy between Holland and England in regard to the mortality from cancer of the

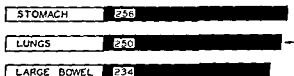


CHART 2 Cancer of the bronchus stomach and large bowel in the male

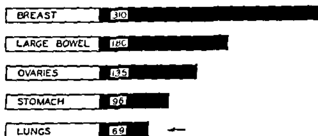


CHART 3 Cancer of the bronchus and cancer of other organs in the female

breast and uterus it is nearly twice as high for English women as for Dutch women A committee of statisticians under the auspices of the League of Nations had undertaken to collect detailed statistics with the object of finding the reason for the difference The conclusion reached was (1) Though there is a great difference in the mortality from cancer of the breast and uterus between the two countries, there is no such difference in the *total* mortality from cancer, which in fact is nearly the same in both countries (2) There is among Dutch women a much higher mortality from cancer of the stomach and intestines than among English women

Age

The age incidence of bronchiogenic cancer is the same as for cancer of other organs In 4 307 cases compiled by Ochsner and DeBakey from the

literature, 1,470, or 34.1 per cent, occurred between the ages of 50 and 59; 1,093, or 25.4 per cent, between 40 and 49; 861, or 20 per cent, between the ages of 60 and 69. At the Glasgow Infirmary Dick found five patients 20 to 29 years old; ten, 30 to 39; thirty-seven, 40 to 49; forty-eight, 50 to 59; twenty-eight, 60 to 69; and three, 70 to 79. More than 80 per cent of Halpert's patients were in the sixth decade or older.

The age incidence of my patients is given in table 9.

TABLE 9

Age Incidence of Bronchiogenic Cancer

AGE	NUMBER OF CASES	
	Males	Females
30–34	6	4
35–39	6	4
40–44	12	13
45–49	23	5
50–54	39	11
55–59	53	7
60–64	43	7
65–69	41	9
70–74	13	5
75–79	8	2
80–84	3	2
85–90	3	0
Total	250	69

The occurrence of bronchiogenic cancer in young persons and even in children has been reported.

Site

The right lung is more often affected by bronchiogenic cancer than the left. Of 4,732 cases collected from the literature by Ochsner, 2,761, or 58.3 per cent, were located in the right lung and 1,971, or 41.6 per cent, in the left. Of 138 cases reported by Shick, 82, or 60.9 per cent, occurred on the right side and 55, or 39 per cent, on the left. Moersch and Tinney found 241 cancers in the right lung and 122 in the left. Of the 319 cases studied at the Montefiore Hospital, 183, or 57.3 per cent, were on the right side and 136, or 42.7 per cent, on the left.

Race

The susceptibility of various races to cancer has been widely discussed and a few decades ago it was stated that Jews are relatively immune to this

cervical and ovarian cancers is in the first half of the fifth decade (40 to 44) i e , ten to fifteen years earlier The prevalence of pulmonary cancer in man may possibly be due to the fact that in the female cancer of the genital organs, which occurs with greater frequency at an earlier age, 'protects" them against the subsequent development of carcinoma of the respiratory organs either by causing death of the patient before the pulmonary neoplasm has had time to develop or (in case of survival) by creating a virtual immunity" or resistance to the development of a new cancer

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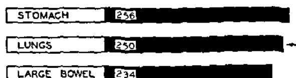


CHART 2 Cancer of the bronchus stomach and large bowel in the male

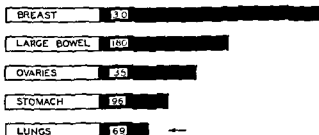


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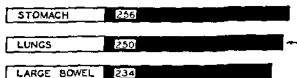


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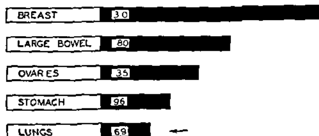


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Tripolli and Holland reported that during a twenty and a half year period, 576,810 patients over 12 years of age were admitted to Charity Hospital in New Orleans, of whom 321,709 were white (157,189 male and 164,520 female) and 255,101 colored (109,014 male, 146,087 female). The race incidence of 195 patients with bronchogenic cancer as given by these authors is shown in table 10.

From this table it will be seen that of the 195 cases of pulmonary carcinoma, 130 occurred in white patients (116 males, 14 females) and 65 in colored (55 males, 10 females). The incidence of white patients at the Charity Hospital, New Orleans, is thus more than twice the Negro incidence.

In Chicago the incidence in white persons is 1.3 times commoner than in colored, according to Steiner. The author does not add much significance to his figures in view of the small number of Negroes on whom necropsies were performed (6.1 per cent).

TABLE 10

Race Incidence of Bronchogenic Cancer at the Charity Hospital, New Orleans

White	130	White males	116
Colored	65	White females	14
Males	171	Colored males	55
Females	24	Colored females	10

Quinland stated that bronchogenic cancer is not uncommon among American Negroes.

As economic, cultural and health conditions (longevity) of the American Negro vary from the White, figures should be accepted with reservation.

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malignant disease Recently it was asserted that cancer of the breast is rare in Japanese women It also was affirmed that so-called wild and uncivilized races are resistant to malignant diseases

More recent investigations failed, however, to substantiate claims that ethnic derivation is a factor of significance Sorsby analyzed the vital statistics of London Venice, Budapest Warsaw and Leningrad and arrived at the conclusion that the incidence of cancer among Jews in any city follows closely that obtaining among their fellow citizens There is a closer relationship between the Jews and non Jews of any particular city than between the Jews of different cities The resistance of Japanese women to mammary cancer too is no longer entertained, and the rarity of malignant diseases among the backward nations is disproved In French Morocco for instance according to Dekester all varieties and locations of cancer are encountered The opinion that cancer is rare in the warm countries should be abandoned In Tunis Lascas ade found that cancer is as frequent among Arabs as among Europeans The deeper one penetrates into the milieu of the natives the more one finds malignant tumors' wrote Lacassade The English Imperial Research Fund Expedition and the *Deutsche Zentralkomitte fur Krebsforschung* found cancer in the Himalaya in New Guinea in the Islands of the Pacific of Samoa and Western Africa in the same form as seen in Europe Mouchet and Gerard affirmed that the Negroes from Central Africa are not only not refractory to cancer but one finds among them all the varieties of cancer seen in Europe

The study on the incidence of bronchiogenic cancer among the colored population of America has been barely touched although the field for such an investigation seems to be propitious Arkin and Wagner found at the Cooks County Hospital that 9 per cent of 135 patients with cancer of the lung were colored The number of Negro patients in that hospital constitutes about 30 per cent Rosedale and McKay found 51 white and 6 colored patients with primary cancer of the lung at the Buffalo City Hospital The figures correspond according to them to the division of the two races in Buffalo

Stein and Joslin found at the Hines Hospital Illinois 154 white and 10 colored patients Of 100 patients who died of bronchiogenic cancer at the Johns Hopkins and Baltimore City Hospitals 68 were white and 32 colored There were 62 white males and 6 white females, 26 colored males and 6 colored females (King and Ford)

Halpert and Tripolli and Holland studied the hospital and post mortem cases from the Charity Hospital at New Orleans Louisiana In the total autopsy material there were 5 635 males (2 610 white and 3 025 colored) and 3 227 females (1,228 white and 1,999 colored), a percentage of almost 2 to 1 Bronchiogenic cancer was found in 123 men (73 white and 50

colored) and in 12 women (8 white and 4 colored), a proportion of about 10 to 1

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CHAPTER II

PATHOLOGIC ANATOMY, HISTOGENESES CLASSIFICATION

THE BRONCHIOGENIC ORIGIN OF PULMONARY CANCER

Histogenetically primary carcinoma of the lung has been divided into three groups according to the epithelial units which the lungs have been considered to have (1) the epithelium lining the bronchi, (2) the epithelial cells which form the mucous glands, and (3) the epithelium said to line the pulmonary alveoli (the walls of the air sacs) Some observers have also based their genetic discrimination on the gross appearance of the tumor Ewing who classified the tumor into the aforementioned groups stated that the *combination of the clinical history, gross anatomy and histologic structure* will furnish a reasonably certain and acceptable histogenic classification This however cannot be relied upon Those who have studied primary pulmonary cancer are familiar with the protean clinical manifestations of this malignant disease The gross anatomy in this cancer as that of other organs will hardly furnish criteria as to the particular histologic structure which gave origin to the growth The microscopic features of a fully developed pulmonary tumor will point to its histogenesis in exceptional cases only, the morphology of the neoplastic cells varies from one tumor to another (columnar, cuboidal spindle shaped squamous epithelial cells basal cells), and even in the same tumor their form may vary from area to area

Many difficulties are encountered in the genetic tracing of a primary pulmonary cancer Most observers are critical as to the existence of tumors having their origin in the alveolar cells, and some (Letulle) do not include in their classification tumors originating in the mucous glands

Of particular interest are blastomas said to originate from the cells lining the pulmonary alveoli (so called respiratory epithelium)

Cancer Originating from Cells Lining the Alveolar Wall Passler (1896) was the first to give a comprehensive discussion of the question and also to review 54 cases of primary cancer of the lung which he found at that period in the literature He reached the conclusion that of this number 47 originated, in all probability, in the bronchial mucosa, while in the others, the histogenesis could not be established He stated, moreover, that cancers having their origin in the pulmonary parenchyma are unknown, or at least that the nonparticipation of the bronchial epithelium in these cases could not be excluded Domeny (1902) thought that tumors made up of small

and large nodules composed of small polymorphic cells forming "pearls" are of alveolar origin Other pathologists claimed that squamous epithelial tumors usually originate in the alveolar cells (Beitzke)

In 1912, Adler published his monograph containing a review of 374 cases of primary carcinoma of the lungs He was of the opinion that the great majority of primary carcinomas of the lungs develop from the bronchi, and that a cancer of the lung is, strictly speaking, a bronchial carcinoma

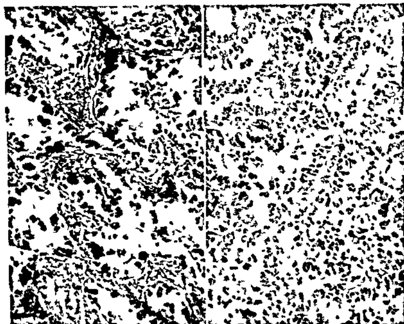


FIG 2 So-called alveolar cell carcinoma The walls of the air sacs are lined by cancer cells

Nevertheless, he admitted the existence of alveolar cell tumors which are built up "not of flat but of cylindrical epithelium" More recent observers stated that in cases where the alveolar septums are lined by neoplastic cells the tumor has originated in the "respiratory epithelium Accordingly they called it 'alveolar cell tumor" (fig 2) They stressed the view that normally the pulmonary septa are lined by an inconspicuous layer of epithelial cells which grow, proliferate and assume a cuboidal shape in inflammatory and fibrogenic conditions The alveolar cell tumors they asserted, originate from these cells, usually in multiple points throughout the lung

However, investigation reveals that the cuboidal cells have penetrated into the air sacs from the bronchioles (fig 3) Experimental and clinical studies in this matter have led the author to the conclusion that the walls of



FIG 3 Showing newly formed alveolar structures in a case of organizing influenza pneumonia The cuboidal cells lining the "alveoli" are offshoots of proliferated bronchiolar epithelium

the alveoli are virtually "naked" (figs 4 and 5) and that the cells found in groups along the walls of the air sacs are not epithelial but most likely mesenchymal in origin and consequently could not be expected to produce carcinoma If

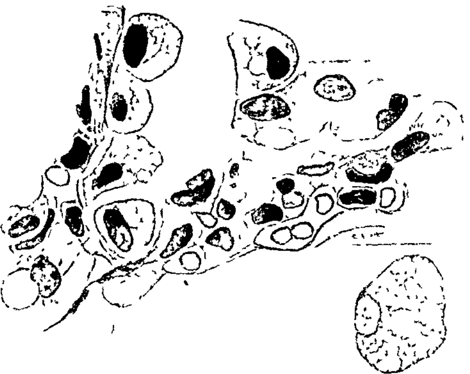


Fig 4 Showing a section of lung from a rabbit that received mineral oil via the trachea The foam cells are mesenchymal macrophages Note the similarity between the cells lining the septum and those lying free in the lumen For comparison a macrophage from the spleen is shown in the inset

one excludes the alveoli as a possible source of carcinoma, the mucous glands of the bronchi remain to be considered

Cancer Originating from the Mucous Glands The mucous glands are structures that lie underneath the bronchial *membrana basalis* Made up of epithelial cells they are considered liable to transform themselves into an



Fig 5 Showing alveoli from rabbits lung infected with tubercle bacilli via the trachea The reaction is confined to the cells of the septums they increased in size grew in number and detached themselves from the wall to form the intraalveolar exudate

epithelial malignant new growth However, Letulle did not include such a variety of tumors in his classification, and the few cases reported in literature which hold that the condition was believed to have originated from these units are wholly unconvincing No one has ever observed an early cancer of this kind, and the criteria, such as the glandular structure as well

as the presence of mucus, which are supposedly characteristic of these neoplasms, in reality distinguish a great many tumors originating from organs that normally form no mucous material

In brief clinical, pathologic and experimental observations support the conception that primary carcinoma of the lungs is only bronchiogenic in origin

REGENERATION OF BRONCHIAL EPITHELIUM AND PULMONARY CANCER

The genesis of cancer is a matter of discussion Apparently a malignant disease in the lungs results from cancerization of the somatic cell First individual cells may acquire the disease, leading to their anarchic growth Second, a local malignant condition may possibly be due to a systemic bodily imbalance of some kind It is probable that both conditions are required for the development of the malady, but many observers are still not certain whether a fully differentiated epithelial cell is liable to become cancerous

It is well established that one of the factors leading to the development of cancer is chronic inflammation (irritation) which causes degeneration of cells followed by an excessive regeneration However, in the lungs the columnar epithelial cells lining the bronchi have not been observed in a state of regeneration

Pathologists have emphasized the fact that neoplasms usually originate from cells which are not fully differentiated They believed that in every organ there exist embryonal centers" (physiologic centers of proliferation) which serve as a point of departure for tumors The problem is complicated because with the methods of observation at present the actual metamorphosis of a somatic cell into a malignant cell has not been observed The skepticism is therefore based on the observations (1) that a fully differentiated cell is usually apotent," and (2) that regeneration which is a forerunner of a malignant condition is performed in most instances by cells other than those which appear at first glance to be affected by the noxious agent The skin is a case in point In the presence of damage to this structure regeneration of the cutaneous tissue occurs only by virtue of the basal cells which are post-embryonic undifferentiated cells, but when these cells, too have been damaged a skin graft is required for the repair of the defect

The lining of the bronchi and their divisions is made up of three different types of cells columnar ciliated cells, goblet cells, and basal cells a variety of small oval cells having a narrow cytoplasm and a nucleus rich in chromatin The last mentioned lie close to the basal membrane, they do not form the uninterrupted syncytium observed in the skin, but are irregularly scattered forming cellular agglomerations Observation reveals that in the

respiratory tract the process of regeneration takes place by virtue of these basal cells which are endowed apparently with latent developmental potentialities (fig 6)

In chronic bronchopulmonary diseases with damage to the bronchial epithelium one often notices that instead of the ciliated epithelium there appear cuboidal cells superimposed by many layers of transitional epithelial cells which have originated from the pre existing basal cells Likewise in inflammatory *processes the cells lining the smaller bronchioles have a tendency* to invade the surrounding tissue forming tubular structures (fig 3) This was erroneously described as pulmonary alveoli lined by alveolar wall



Fig 6 Basal cells of bronchial mucosa in a stage of early proliferation

cells which have reclaimed their embryonic cuboidal aspect (regressive metaplasia) The epithelium of the proliferated bronchioles also not infrequently invades tuberculous or bronchiectatic cavities lining their wall They proliferate and invade the bronchial mucous glands as I have observed in man and also in experiments on cats and rabbits with the intratracheal injection of oils In all instances when the ciliated columnar cells *were destroyed or damaged* the basal cells only showed active regeneration (mitoses and proliferation) they formed many layers of small cuboidal or oat shaped cells and also invaded the alveoli

Experimental and clinical investigations show that cancer in man is usually preceded by a process of regeneration The development of epithelioma in areas subjected to roentgen rays the occurrence of epithelioma of the lip in pipe smokers and tar and paraffin *cancers* are widely known Observa

tion has shown that cancer of the lungs too, usually follows a long standing chronic inflammation Ewing has expressed the belief that the chief etiologic factor of carcinoma of the lungs is tuberculosis, other observers have found it in patients with bronchiectasis or with pulmonary syphilis Tuberculosis syphilis and other chronic inflammatory processes cause damage of the bronchial mucosa followed by excessive (pathologic) regeneration which eventually leads to the development of an epithelial malignant disease

The apparent lack of activity in the process of bronchial repair on the part of the ciliated columnar epithelium in the presence of an active basal cell proliferation leads the author to favor the conception that only the latter cells are concerned in the genesis of an epithelial malignant disease in the lungs

METAPLASIA AND PULMONARY CANCER

Post mortem material reveals that the majority of all pulmonary tumors are of the squamous cell type Since normally such cells are absent in the lungs, the origin of these tumors was said to be due to a conversion of the ciliated columnar cells into the squamous epithelial variety The condition is therefore designated as metaplasia (fig 7) This conception of a direct transformation of one well differentiated tissue into another equally well differentiated but morphologically and functionally different was advanced for the first time by Virchow This concept however was not borne out by close observation In the first place as already noted it is improbable that the apotent ciliated columnar epithelium is able to transform itself into any other variety of cell Another point was raised by Wells (1929) who said

> The formation of metaplastic squamous epithelium brings forward two puzzling topics one chemical the other embryologic The chemical peculiarity is that squamous epithelium is characterized by the formation of keratin which is a definite chemical compound formed normally as far as is known by the cells of ectodermal origin including the neurokeratin of the central nervous system When cells of endodermal origin such as those lining the renal pelvis or the uterus take on the function of forming this peculiar insoluble sulphur rich indigestible protective chemical keratin they have assumed a chemical function which seems to be far removed from their normal capacity Hence we must conclude that metaplasia involves not only a morphologic but a chemical transformation of cells
>
> For tumor pathology another problem arises When cells assume the proliferative activity that is characteristic of malignant disease they usually lose their more recently acquired function and retake chiefly the simple

vegetative function of proliferation But when a transitional or columnar epithelial surface becomes squamous through metaplasia and the same protracted irritation that produced the metaplasia continues until cancer results we find that the newly acquired property of forming keratin has become fixed and the cancer is a keratinizing squamous cell carcinoma One would expect the epithelium to approach its original simpler embryonal character rather than exhibit and retain so profound and recently acquired an alteration as the production of keratin'

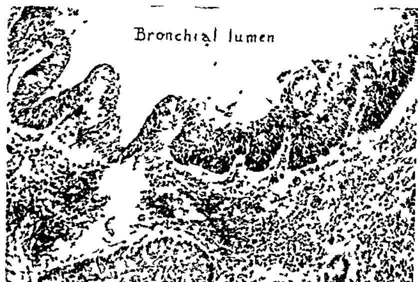
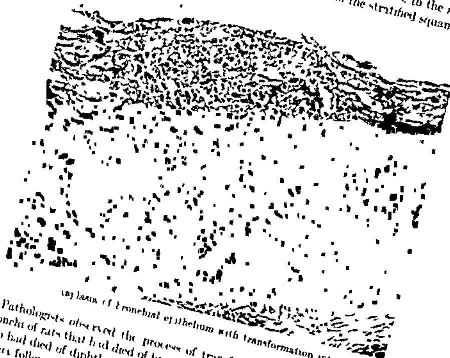


Fig 7 Metaplasia of bronchial epithelium

Today the original conception of Virchow of a direct metaplasia has received a new interpretation Observers deny the authenticity of a direct transformation of the endodermal columnar cell into an ectodermal squ ous epithelial cell Indeed there is no such thing as direct metaplasia the persistence of cells only those cells which are endowed with dorr developmental potentialities may undergo new changes Those cells l ever which have become entirely apotent do not regenerate and are apt to be transformed into a new cellular type Most pathologists re the so called metaplasia as a complicated biologic process of regenera with new formation of cells (neoplastic phase) which is ultimately follo by a differentiation (metaplastic phase) Cells with embryonic or p embryonic potentialities are liable to such a metamorphosis whereas ciliated columnar epithelium lining the bronchi is a fully differentiated therefore a nonreversible cell

What, then, is the origin in the lung of the "foreign" squamous epithelial cells?

The idea of a few observers that this cell is apparently an embryonic rest could not be corroborated by diligent investigators. Clinico-pathologic and experimental studies convincingly point to another source. It would appear that the basal cells already referred to which lie close to the *membrana basalis* of the bronchus are the progenitors of the stratified squamous epithelium (fig. 8).



…lasia of bronchial epithelium with transformation into cancer

Pathologists observed the process of transformation of this cell in the bronchi of rats that had died of bronchopneumonia, in the lungs of children who had died of diphtheria or measles, and persons who had died of pneumonia following influenza.

Apparently this pathologic process occurs in numerous broncho-pulmonary diseases (influenza, pneumonia, whooping cough).

The peculiar character of the differentiation of these cells into squamous epithelium is interpreted in the light of the ontogenesis of the tissue in question. From an embryologic standpoint the tracheobronchial tree and the esophagus represent two sister organs, and their development goes parallel. In the earliest stages of development the esophagus is lined with

one layer of cuboidal cells, which at the fifth week double and at the tenth acquires goblet cells and ciliated columnar epithelial cells Whereas in the bronchi the development ends at this phase, in the esophagus these cells degenerate and desquamate, being subsequently replaced by a transitional epithelium and finally by a stratified squamous epithelium It is assumed that in pathologic processes the bronchus, in its regenerative attempt merely reaches in the adult the stage which the esophagus has attained as an embryo

It will be seen that the process is not a transformation of the adult columnar epithelium into a squamous type, but that a development of undifferentiated cells followed by proliferation and differentiation has occurred The phenomenon is not a metaplasia, but a protoplasia (in direct metaplasia)

Briefly, then, the process of repair or regeneration in the bronchi is performed by the bronchial basal cell only In physiologic repair, these cells differentiate merely into the normal lining of the bronchus But when the process is pathologic, their fate depends in all probability on the nature of the stimulus and also upon the "resistance" of the host Thus they may differentiate into metaplastic islands and so remain indefinitely, or they may develop into a malignant condition In fact, most pathologists regard the phenomenon of metaplasia a precancerous stage

CANCERIZATION

Cancerization occurs through transformation of the basal cells into malignant cells directly or indirectly by way of metaplasia, as detailed above

The inauguration of cancer is characterized by erosion and ulceration of the normal mucous membrane of the bronchus which is replaced by tumor (fig 9) How long the neoplastic cells remain in situ before they begin to spread has not been ascertained In cancer other than the lung emphasis has been placed on the hidden character of early carcinomatous lesions and the absence of gross anatomic evidence of a malignant lesion In the skin, for example, the interval between the inception of the cutaneous cancer and the appearance of clinically recognizable cancer oscillated between one and ten years In carcinoma of the cervix uteri there exists a long period of latency before invasion by the cancerous cells and a still longer period before the carcinoma is manifest

Bronchi of all sizes are apt to become cancerous But, as elsewhere stated, in the majority of cases the growth starts in the main stem or in a larger branch of the main bronchus, at or near the hilus In about 15 per cent of cases the neoplasm starts in a small bronchiole close to the

periphery of the lung In the main stem bronchus the cancer usually starts about 4 cm below the bifurcation of the trachea This is of importance from the surgical standpoint, for the nearer the tumor is to the bifurcation the more difficult is the amputation of the affected lung In deed, a minute cancer in the close vicinity of the bifurcation represents an unsurmountable surgical problem

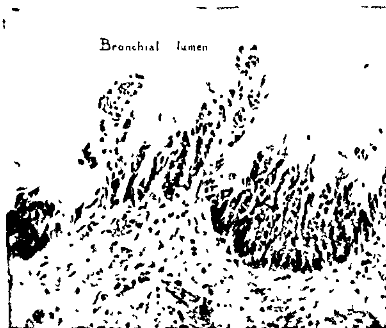


Fig 9 Early carcinomatous proliferation

The more frequent involvement of the right lung by cancer was attributed to the fact that the right main bronchus is wider shorter and more horizontal than the left thus facilitating the penetration of irritating (carcinogenic) substances into this lung It is also conjectured that, being larger in size, the right lung is thereby entitled to a greater share of cancer '

When the tumor is on the left side it is a short distance from the recurrent laryngeal nerve as it passes around the aorta The affection of this nerve induces paralysis of the vocal cord and hoarseness

A strict estimation of the involvement of individual lobes is often beset with difficulties Nevertheless it was calculated that the right upper

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lobe is affected in about 27 per cent, the right middle in about 3 per cent, the right lower in 23 per cent, the left upper lobe in 20 per cent, the left lower lobe in 14 per cent

From the bronchi the tumor spreads upwards and downwards yielding upper, middle or lower lobe cancer, respectively

Classification The chronicity, the dynamic nature and the mode of spread of bronchiogenic cancer make attempts to accurately trace its life history in most instances hazardous Probably because of this physicians have failed to produce a clinical classification of their own and have adopted concepts suggested by pathologists whose findings were based on post mortem observations

Weller distinguished three main types (1) type associated with the hilus, (2) a nodular type developing in the parenchyma, and (3), a diffuse type

Jaffé identified four types (1) the central or hilus which starts in the main bronchus, (2) the intermediary originating from a bronchus of the 3rd, 4th or 5th order, (3) the peripheral which starts underneath the pleura, and (4), the diffuse type

Frissell and Knox recognized five types (1), central or hilus type (2), nodular parenchymatous, (3), peripheral (4), diffuse (5), bilateral miliary

Rabin and Neuhof divided their cases into two groups (1) the central or non circumscribed type originating in the main bronchus and visible with the bronchoscope, (2) the peripheral or circumscribed originating from a small bronchus and not visible with the bronchoscope They stated that the second variety of tumor can be approached surgically with greater success and that as a rule it offers a better prognosis than the first Graham, on the other hand found that tumors of the major bronchi give symptoms earlier extend more slowly, are more amenable to surgical treatment and are less rapidly fatal

While it is true that cancers of the major bronchi manifest themselves earlier than those of the minor, they are, however, liable to induce more extensive secondary changes in the pulmonary parenchyma When a major bronchus is obstructed it leads to collapse of the entire lobe or lung whereas the occlusion of a small bronchiole induces segmental or lobular damage only

On gross inspection bronchiogenic cancer like that of other organs is grayish white and firm It early undergoes changes due to secondary infection the lungs are the only visceral organs in direct connection with the outside world they readily become a prey to aerobic and anaerobic pathogens Infection is facilitated by insufficiency in the supply of blood, particularly of the central parts of the growth

CAVITY FORMATION

Necrosis is characteristic of all cancers, but the formation of voluminous cavities with fluid levels is a trait observed in bronchiogenic cancer only (fig 10) The cavity may be so large as to give the impression of an abscess and totally eclipse the new growth Ameuille was the first to observe a



Fig 10 Carcinoma of the bronchus to the lower lobe with cavity formation

patient whose symptomatology and roentgen ray films were compatible with an abscess of the lung During thoracotomy, out of curiosity, Ameuille examined the pus under the microscope and was surprised to find a carcinoma It was estimated that 15 to 20 per cent of pulmonary cancers show large central cavities (Cancer of the lung with cavity formation)

MACROSCOPIC CLASSIFICATION

The size and structure of the lung predispose to expansion of the growth and to a multiplicity of patterns, particularly in the slowly growing types

The shape of the tumor is often affected by an early collapse of the lung pleural exudate pulmonary fibrosis or a slumbering infection When cancer reaches an area of infection with necrosis it makes a detour Cancer cells do not invade caseated tissue or a tuberculous cavity filled with



FIG 11 Hilus type of bronchiogenic carcinoma

caseated matter, they spread along the wall of a healed or healing cavity and invade the wall itself, but shun the cheesy area

It is desirable to classify the tumor into three types

1 Hilus type originating in the main bronchus or in a large branch of the main bronchus, at or near the root of the lung About 85 per cent of

bronchiogenic cancers originate in these locations They are usually accessible to bronchoscopic inspection and can be removed surgically when not too close to the bifurcation of the trachea

2 Peripheral or bronchiolar originating at the periphery in a small branch of a bronchus In the early stages they are seen as round dense

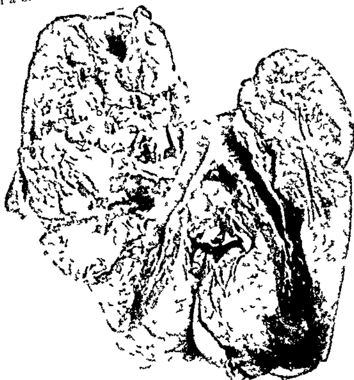


FIG 12 Lobar type of bronchiogenic carcinoma

shadows often mistaken for tuberculosis The practice of mass roentgenographic surveys has lead to the discovery of many asymptomatic cases of this type These tumors are beyond the reach of the bronchoscope but are considered to be more amenable to surgical intervention

3 Apical or superior pulmonary sulcus tumor originating in a bronchiole at the very apex of the lung detailed in Chapter VII

The hilus type is the one that ultimately assumes various aspects lobar, nodular, infiltrative, miliary (figs 11, 12, 13, 14)



FIG 13 Nodular type of carcinoma of the bronchus

The rate of growth of the tumor and the occurrence of metastases depend not so much on topography or appearance as on factors which are not fully understood The duration of the illness in the various types respectively, is about the same



FIG 14 Infiltrating type of carcinoma of the bronchus

MICROSCOPIC CLASSIFICATION

Although histologically bronchiogenic cancer possesses a large degree of pleomorphism certain cellular types predominate

1 Squamous epithelial cell a keratinizing b non keratinizing c giant cell medullary d oat cell e anaplastic

2 Adeno-carcinoma a simple b papillary c mucocellular

3 Round cell (figs 15-22)

The squamous cell cancer occurred in 73 per cent of cases adeno carcinoma in 12 per cent other types in 15 per cent Adeno-carcinoma was observed five times more frequently in women than in men While in the entire series it occurred in 12 per cent its incidence in the female amounted to 32 per cent in the male to only 6 per cent In the two sexes



Fig 15 Stratified squamous cell carcinoma with pearl formation

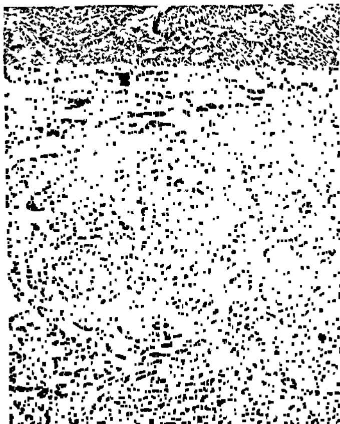


FIG 16 Basal (squamous) cell carcinoma of the bronchus

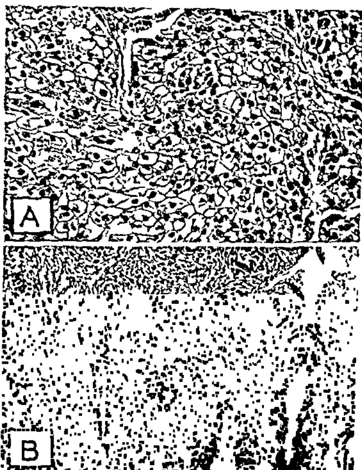


Fig 17 A, squamous cell carcinoma with clear cells, B, squamous cell carcinoma made up of spindle cells tending to form rosette like structures

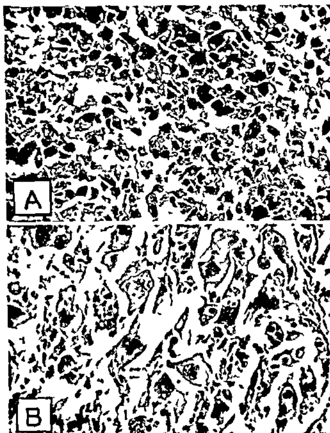


FIG 18 A squamous cell carcinoma undifferentiated B giant (squamous) cell carcinoma



Fig 19 So called oat cell carcinoma

Fig 20 Papillary adeno carcinoma



FIG 21 Muco cellular adeno carcinoma Section taken from a metastasis to the bone



FIG 22 Round cell carcinoma tumor cells in the lumen of a pulmonary vein

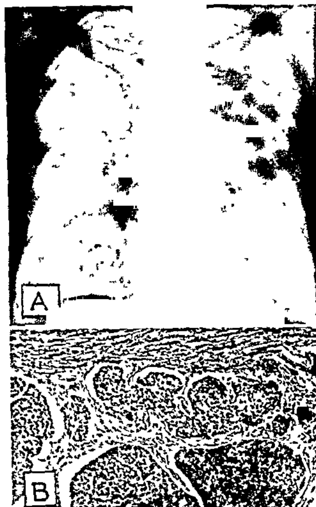


FIG 23 A squamous cell carcinoma of the bronchus to the left upper lobe in a man of 31 metastatic to mediastinal and periaortic lymph nodes contralateral lung epicardium heart muscle and stomach B the microphotograph shows metastasis in the epicardium

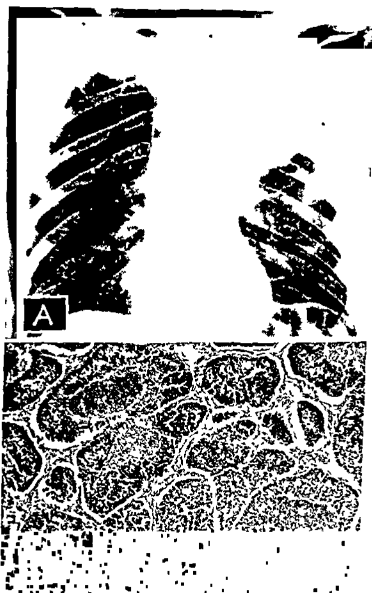


FIG 24 Squamous cell carcinoma in a man of 71, metastatic to pleurae of both lungs, adrenal, liver and right heart



Fig 25 Squamous cell carcinoma to the bronchus of the right upper lobe in a man 5? metastatic to hilus lymph nodes contralateral lung liver kidneys thyroid adrenals and bones



Fig 26 Squamous cell carcinoma in a man of 39, metastatic to pleura liver, right adrenal and pelvic bones

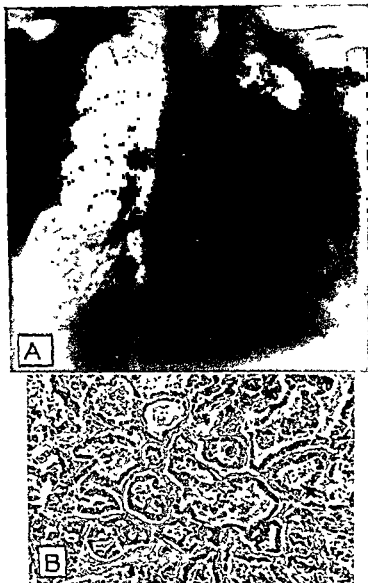


FIG 27 Adeno carcinoma of left lower lobe in a woman of 34 metastatic to tracheo bronchial lymph nodes contralateral lung pleura left adrenal and bones



FIG 28 A, adeno carcinoma of left lung with cavity formation in a man of 49 metastatic to liver and brain Hydrothorax (arrow) B the microphotograph is from a metastasis to the liver

respectively, it displayed more malignant tendencies than other varieties as evidenced by the clinical course and the distribution of metastases

The interdependence between the clinical course of the disease and the histological structure is debatable Some observers stated that adenocarcinoma has a strong tendency to invade the central nervous system adrenals kidney, contralateral lung and to some extent the liver (Simpson) It also was asserted that there exists a distinct difference in the tendency to metastasize depending on the cell type the oat-cell types are vigorously metastasizing tumors whereas the squamous cell type is infiltrating and relatively non metastasizing (Koletsky) These findings should be accepted with reservations There is no close connection between the degree of cellular differentiation and the tendency to metastasize Anaplastic cancers may remain confined to the lungs whereas the differentiated may become disseminated (figs 23 28)

CHANGES IN THE LUNG AFFECTED BY CANCER

All elements of the pulmonary tissue not invaded by tumor show damage As a result of the involvement of the bronchus with its partial and eventually complete occlusion there often occurs an obstructive atelectasis and an obstructive emphysema The emphysema at times forms bullae (bullous emphysema) which may attain large dimensions Occasionally they rupture inducing pneumothorax and empyema A diagnostic pneumothorax advocated by some physicians should be recurred to with great caution for fear of these complications

Atelectasis of the entire lung or of one lobe occurs with much greater frequency than emphysema In very many cases it is an early sign pointing toward the presence of a bronchial occlusion probably of a neoplastic nature Atelectasis is often complicated by infection (pneumonitis) with the formation of abscesses and bronchiectasis

Damage to the bronchi consist in degenerative and metaplastic changes of the mucous membrane An organizing pneumonitis affects the bronchi causing an obliterating bronchitis or bronchiolitis

The blood vessels in the vicinity of the tumor show changes consisting in thickening of their walls and in endovascular changes such as intimal thickening and endo arteritis obliterans In areas of the lung remote from the tumor the changes are largely related to atelectasis and infection

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ALVEOLAR CELL CARCINOMA AND ADENOMATOSIS OF THE LUNGS

Nomenclature Pulmonary Adenomatosis, Multiple Pulmonary Adenomatosis, Pulmonary Alveolar Adenomatosis *Jaagsiekte*

Clinical and Pathological Features The disease is of interest because microscopically it resembles so called Alveolar Cell Carcinoma Bonne *considered it a malignant disease and suggested the name Carcinosis* Simon stated Pulmonary adenomatosis and alveolar cell tumors may be regarded as unusual forms of pulmonary carcinoma presumably arising from alveolar lining cells It is also of interest that the disease in man is a replica of epizootic adenomatosis in sheep (Jaagsiekte Montana Progressive Pneumonia in Sheep)

The disease is characterized by cough productive of watery or mucoid sputum steady loss of weight low grade fever anorexia and progressive dyspnea

On roentgenologic examination one finds wide areas of consolidation or multiple diffuse soft mottlings confined to the entire or to parts of the lungs only The sputum and other laboratory studies yielded negative results

At the post mortem examination one or both lungs showed either consolidation occupying most of one or both lungs resembling lobar pneumonia in the stage of gray hepatization or multiple nodules varying in size from a few millimeters to one centimeter scattered throughout both lungs The bronchi were normal and no adhesions were found between the lobes or between the pleurae The lymph nodes and the visceral organs outside the lungs contained no disease

Microscopically the pulmonary alveoli were found to be uniformly lined by one layer of non ciliated mucous forming columnar or cuboidal epithelium often forming papillary projections The cells showed no features compatible with malignant disease

Pathogenesis Epizootic adenomatosis, or Jaagsiekte has been the object of multiple studies which failed to isolate a pathogen or to transmit the disease experimentally from animal to animal Nevertheless the contention was that it is a contagious disease caused by a filtrable virus Dungal pointed out that in Iceland where it is epizootic among sheep it has never been contracted by shepherds who are in constant contact with the animals Wood and Pierson performed a lobectomy on a man for cavities in the

right lower lobe, and what grossly seemed to be non caseating disseminated miliary tuberculosis, proved histologically to be adenomatosis Their efforts to demonstrate a virus in the removed lobe and, post mortem, in the rest of the lung, have failed Although quasi similar histologically, the pathogenic identity of epizootic adenomatosis (Jaagsiekte) and human adenomatosis has not been demonstrated

The resemblance between adenomatosis in man and so called alveolar cell carcinoma is also histological only in both conditions the walls of the pulmonary alveoli are lined by a single row of columnar or cuboidal cells However, while in adenomatosis the cells are benign, in alveolar cancer they are malignant

Source of Cells in Adenomatosis and Alveolar cell Cancer What interested observers most was the source of the cells found along the walls of the air sacs in the pathogenic as well as in the malignant disease There are two schools of thought

1 In epizootic as well as in human adenomatosis the cells normally lining the alveolar septa are activated by a noxious factor (? virus), proliferate simultaneously in various parts of the lungs, giving the picture of multiple or multicentric adenomatosis

In alveolar cell carcinoma, they stated, the respiratory epithelium has become cancerous in multiple areas (or throughout the entire lung) simultaneously Hence the designation of (multicentric) alveolar cell carcinoma Oberndorfer, whose article is often referred to wrote "In both lungs simultaneously there occurred (in his case) an acute mutation of the alveolar epithelium with a tendency toward tumor formation " ("An verscheiden sten Stellen beider Lungen gleichzeitige und Akut auftretende Mutation der Alveolar-epithels mit blastomatosen Tendenz ") Briese (another often quoted author) based his opinion of the alveolar cell origin of the cancer on their columnar shape, formation of mucous and glandular arrangement " The futility of these criteria has been detailed in another part of this treatise

2 In epizootic as well as in human adenomatosis the epithelial cells of the terminal bronchioles are primarily affected by the unknown pathogen Under the influence of this factor they begin to proliferate and sprout into the pulmonary alveoli, which naked" walls they line forming gland like units, adenomatosis The abnormal epithelium of adenomatosis" wrote Paul and Ritchie in their report of five cases, "is derived, in some cases at least, from bronchial epithelium In two of (their) five cases there was an intimate relation between the bronchial epithelium and the cellular lining of the adenomatous alveoli "

The aptitude of these cells for proliferation and "ingrowing' into the alveoli in inflammatory and fibrogenic conditions of the lungs has been

frequently noticed (lipid pneumonia, whooping cough, influenza pneumonia)

The fact that no gross tumor was found in the lungs in cases of so-called alveolar cell carcinoma does not sustain the view that the tumor originated in the alveoli It has been repeatedly observed that minute or barely visible cancers yielded voluminous metastases In one of my patients a minute tumor was found in the bronchus with the dissecting microscope after the discovery of large abdominal metastases In another patient a bronchiogenic cancer was discovered after the finding of extensive metastases in the adrenals Mitchel reported a case of primary carcinoma of the thyroid in which the presenting clinical picture was one of pulmonary involvement The metastases in the lungs had apparently occurred early and were profuse The gross and microscopic pulmonary changes bore a resemblance to the so called primary alveolar cell cancer of the lung Herbut observed an adeno-carcinoma of the gall bladder with the gross and histologic alveolar cell distribution in the lungs In a study of 125 cases of metastatic pulmonary carcinoma he found that when the primary tumor was an adeno carcinoma the distribution of metastases in the lung was that of an alveolar cell arrangement

Indeed the cells in diffuse intraalveolar (alveolar cell) cancer should be looked upon not as mutation of the so-called alveolar epithelium but as a widely distributed canalicular metastasis from an invisible (with the naked eye) or overlooked cancer of the bronchus Adenomatosis of the lungs is a pathogenic disease caused in all likelihood by a virus The cells found lining the septa are not aboriginal but are imported from the bronchioles

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Chapter III

ETIOLOGY

As an organ in contact with the outside world the lungs receive dust bacteria, fumes and gases directly from the air As an organ of convergence of the body they are reached by soluble and particulate matter via the systemic circulation Probably due to these facts a multiplicity of causes have been incriminated in the etiology of primary carcinoma of the lung

TUBERCULOSIS

Ewing affirmed that there exists an etiologic relationship between cancer of the bronchus and tuberculosis of the lungs He wrote The chief etiologic factor of primary carcinoma of the lung is tuberculosis

From Bayle s treatise published in 1810 it would appear that already at that period the association of tuberculosis and carcinoma attracted the *attention of physicians However from his discussion on the subject one is led to the conclusion that Bayle an outstanding pathologist and clinician as well as his contemporaries were confused in matters pertaining respectively to tuberculosis and carcinoma and indeed to the symbiosis of the two diseases*

Bayle is universally quoted as the first who recorded a case in which the *two conditions were associated in the same lung A perusal of his report* fails to reveal that he was dealing with the combination His case is herewith presented in condensed form

A man of 72 whose illness was of six weeks duration complained of generalized pains A large nodular liver was palpable As auscultation or percussion of the thorax was not practiced in those years physical findings were not recorded At autopsy the lungs were found to be slightly adherent to the chest wall and except for engorgement appeared normal At the root of the left lung a white shiny mass measuring four fingers in length and two in width was found A few blood capillaries crossed this mass which on compression exuded a creamy matter Here and there this substance as the tissue around it contained tubercles Minute tubercles and small purulent foci were present in all lobes of the lung The liver contained numerous small cancerous nodules

First Authentic Case Antagonism and Exclusion Theories The first case on the subject was published by Pénard in 1846 and concerned a man of 38 whose lungs were filled with encephaloid nodules from apex to base

with tubercles and with cavities Miliary tubercles were found in the spleen "

Walshe, in 1840, stated that "tubercle and cancer possess a sort of repulsion in respect to each other" He based his opinion on the observation of 104 autopsies of patients with cancer, 7 of whom suffered simultaneously from phthisis Rokitansky stated that the two diseases mutually exclude each other (Exclusion theory) while Beneke expressed the opinion that they are mutually antagonistic (Antagonism theory) However, with the advance of knowledge reports of the association of carcinoma and tuberculosis in the same lung began to appear sporadically (Friedlander, 1885, Wolf, 1895, Schwalbe, 1897) The subject was revived by Lubarsch whose autopsy statistics seemed to sustain the earlier assertions made by Walshe, Rokitansky and Beneke Since then clinicians and pathologists have invariably stressed the opinion of the last writers In recent years the Antagonism theory acquired a supporter in the biologist Raymond Pearl who stated that

Only rarely does an active considerable tuberculosis coexist with a malignant neoplasm in the individual, apparently due to a significant antagonism between the two pathologic phenomena which disappears when and if the tuberculosis process retrogresses or heals particularly by the fibroid route "

Personal Observations In the author's material of 319 cases 10 6 per cent showed the pulmonary carcinoma to be associated with tuberculosis of the lungs The dominant type of cancer was the stratified squamous cell There were three epidermoid carcinomas, two adeno-carcinomas, three oat cell cancers and five small round cell cancers The tuberculous lesion was respectively of the fibrotic, fibro cavitary and acute penumonic types

The two diseases in the lungs were associated in different ways

1 Cancer and tuberculosis "collided" in the same lung

2 They were in different parts of the same lung

3 They were in different lungs

While in groups 2 and 3 the association of the two diseases was in all likelihood accidental in group 1 the possiblity of an etiologic relationship could not be excluded

Analysis of the cases points to the view that the tuberculous lesion was of long duration and that the cancer supervened subsequently In individuals with a chronic productive tuberculosis there occurs an active response of tissues by repair, that is by regeneration of the epithelial structures which may culminate into a malignant disease If acute exudative tuberculosis does not bring about the death of the patient before cancer has had time to develop, the reaction of repair or regeneration in



fibrotic and the lung beyond the cavity is atelectatic.

these persons would be so insignificant as to eliminate whatever cancer producing effect they may ordinarily possess.



Fig 30 Cut surface of a lung with a tuberculous cavity filled with carcinomatous tissue

Tuberculous Cavities and Cancer In some cases cancer cells were found lining the wall of a tuberculous cavity (fig 29 C) and in others the cavity was filled with tumor (fig 30) Observation revealed that the malignant disease had originated not in the wall of the cavity as described by some observers, but in the wall of the bronchus wherefrom it penetrated

into the cavity The mechanism of this neoplastic invasion is analogous to the process of penetration of normal cells of the bronchial mucosa into a tuberculous or a bronchiectatic cavity Cavities are usually supplied by bronchi (fig 31) whose mucosa is so badly damaged that it no longer contains ciliated columnar and goblet cells but basal cells only These cells possess remarkable powers of proliferation and serve as the sole source for repair of the bronchial mucous membrane In pathological processes they grow extensively and penetrate neighboring tissues They also invade tuberculous cavities and grow along their fibrous walls This process is known as epithelialization of a cavity The mechanism of cancerization of a tuberculous cavity in bronchiogenic carcinoma is similar

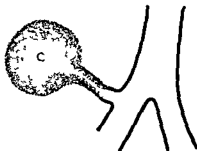


Fig 31 A schematic drawing of the trachea and of a bronchus to the upper lobe penetrating a cavity The stippling represents cancer C cavity

to epithelialization Cancer cells penetrate into the cavity from a cancerous bronchus spread along its wall and fill it

TAR AND DERIVATIVES

The carcinogenic action of tar was demonstrated first by Ichikawa and Yamagiwa who have shown that when the rabbit s ear which is never the seat of a spontaneous tumor is painted for a certain period of time with this chemical it develops a cancer Since then tar has been successfully applied in the causation of cancer of other structures in different animals of which the mouse is the animal of choice The customary technique consists in the application (painting) of tar to several cutaneous areas, the applications spaced at short intervals With the microscope one notices damage to the skin caused by the chemical and excessive regeneration (papillomatous growth) which often culminates in epithelial malignant disease

Tar and Bronchiogenic Cancer An etiologic relationship between tar and bronchiogenic cancer in man was suggested by the accidental finding of

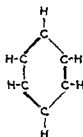
Moller who while studying rats painted with tar found that they had developed cancer of the lung and not of the skin Subsequent experiments on mice by Murphy and Sturm, and by Shabad corroborated Moller's observation Murphy and Sturm did not consider however that inhalation of the tar was the factor which had caused the pulmonary cancer in the rodent They believed that the tar acted only as a factor in lowering the resistance of the mice while the pulmonary cancer was due to irritation by inhaled dust or other particulate matter Shabad excised the cutaneous areas painted with tar but this did not prevent the rodents from developing pulmonary cancers

Following these reports clinicians have incriminated painting of roads with tar in the etiology of primary carcinoma of the lung It was suggested that tar and gasoline, respectively act as chemical irritants inducing malignant disease of the bronchus Campbell by exposing mice to heavy concentration of road dust containing two to three per cent of tar found pulmonary tumors in 74 per cent while in the control group 14 per cent only were affected Mice breathing dust from which tar had been removed with benzene showed 40 per cent of tumors of the lungs

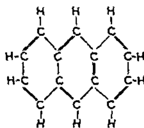
Carcinogenic Hydrocarbons and Tumors of the Lungs Kennaway Cook and their associates demonstrated that the fundamental compound of many tars is anthracene made up of three benzene nuclei (fig 32 A B C) By the addition of a benzene ring to anthracene in 1 2 position one obtains 1 2 bezanthracene By adding a benzene ring to 1 2 bezanthracene in the 5 6 position 1 2 5 6 bezanthracene is obtained (fig 32 D and E) Pyrene is made up of four benzene nuclei (fig 32 F) 3 4 benzpyrene is made up of the addition of a fifth benzene nucleus in the 3 4 position (fig 32 G) The last named is one of the most active carcinogenic hydrocarbons Another powerful carcinogenic hydrocarbon was found in methylcholanthrene a derivative of 1 2 bezanthracene (fig 32 H)

The isolated and synthetized carcinogenic hydrocarbons are crystals or powders soluble in oils fats or benzol respectively They are administered in solution subcutaneously intravenously intraperitoneally orally or as in the case of tar, painted on the skin With the dose currently employed methylcholanthrene (chemically closely related to bile acids) and cholanthrene require about four and 1 2 5 6 dibezanthracene about seven months for the development of a tumor in a mouse animal of choice for the experiment

By the use of these substances pulmonary tumors could be induced in mice almost at will It was discovered however that tumors can be produced with greater ease in those mice that are naturally predisposed to the disease than in those who lack the tendency to develop the tumors spontaneously Greater amounts of the chemical and a much longer



A



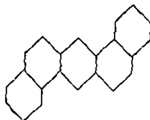
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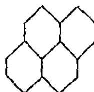
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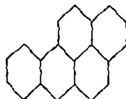
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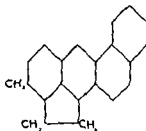
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H

period are required to obtain positive results in the latter group. In strain A mice, natural victims of pulmonary tumors, Shimkin, by intratracheal injection of 0.1 mg. of 1,2,5,6-dibenzanthracene or methylcholanthrene, was able to induce tumors of the lungs in 90 per cent of animals within four months. By using the intravenous route, he obtained pulmonary tumors in 100 per cent of mice of the same strain A.

The reason for the dissimilarity in response to carcinogenic hydrocarbons by different strains of mice was not explained. It was conjectured that the carcinogen probably alters the constitution of the test animal, releases hereditary tendencies, accelerates some processes inherent and genetically determined in the animal (Andervont, Shimkin).

Pulmonary Tumors in Mice and Men. A study of the murine pulmonary tumors so induced revealed their dissemblance to bronchiogenic carcinoma in men. In man, cancer of the lung takes its origin in the basal cells of the bronchial wall, whereas in the mouse the pulmonary tumor is believed *to take origin in the cells of the alveolar septa, although Shabad affirmed* that in most instances they originated in the epithelium of the bronchioles. Since clinical and experimental data are to the effect that the septal alveolar cells are of mesenchymal origin, the pulmonary tumors in mice are probably of mesodermal nature. The tumors transplanted into the subcutaneous tissue often assume a sarcomatous aspect, and the subcutaneously injected carcinogenic hydrocarbons usually induce sarcomas. Also of interest is the fact that the induced pulmonary tumors are usually multiple, scattered over both pulmonic fields, while in man cancer of the lung is a solitary growth. Again, the tumor in the mouse starts just beneath the pleura, grows very slowly and never causes death of the animal. This is not the case in man. Unlike carcinoma, which usually provokes a considerable leucocytic reaction around the neoplasm, the tumor of the mouse causes no outpouring of white cells in the vicinity.

That the murine tumors are probably malignant was suggested from *their not being encapsulated, their local invasiveness (rather expansiveness),* transplantability and ability to metastasize but rarely. They are not referred to as carcinomas but as adenomas or cystoadenomas. As yet they have shed no light on the etiology of bronchiogenic cancer in man.

Tobacco

It is commonly accepted that in order to produce an infectious disease in an animal, the virulence of the germ, the dose of infection material as well as the susceptibility of the host should be taken into account. Moreover, the susceptibility of an animal to a given species of bacterium not infrequently depends upon the route by which the organism is introduced.

The experimental pathologist has only lately begun to realize that the application of some 'irritant' is not alone sufficient always to produce malignant disease, that not every 'irritating' substance will lead to a malignant disease and that even 'verified" cancerogenous agents will not infrequently fail to excite a particular structure to participate in the development of a malignant process

Fibiger, for instance has demonstrated that rats fed with the *Spiroptera neoplastica (Gongylonema neoplasticum)* will acquire cancer of the stomach *while other spirochetes will cause no malignant disease*[1] *Similarly, coal* tar products will induce a cutaneous but not a rectal cancer in mice Again the *Spiroptera neoplastica* leads to an epithelial malignant disease while the *Cysticercus fasciolaris* the larva of the cat tapeworm *Taenia crassicolis* (Bullock and Curtis) induces as a rule a malignant connective tissue tumor of the liver Likewise in grafting malignant tumors it was observed that whereas the inoculations into the brain the anterior chamber of the eye or the muscles will lead in most instances to a vigorous growth of the transplanted neoplasm subcutaneous intravenous and the intraperitoneal grafts will take in from 20 to 25 per cent only The intracutaneous method will yield still less favorable results Apparently the immunobiologic principles which have been involved in the study of infectious diseases deserve to be considered in the study of experimental and spontaneous tumors[2] The carcinogenic substance the host and the particular *organ or structure attacked should be considered*

Recently a few investigators made the suggestion that smoking of tobacco is in all likelihood a causative factor The fact that bronchiogenic

[1] Fibiger was the first to induce cancer in rats and mice with the *Gongylonema neoplasticum* which belongs to the group of nematodes and not spirochetes as was formerly thought The nematode hatches its eggs in an intermediary host—the *Periplaneta americana Periplaneta orientalis* and also *Blatta americana* (species of cockroaches) By feeding rats with infected cockroaches or with their musculature which harbors the parasite Fibiger observed that the larvae of the nematodes free themselves in the gastric cavity of the rodents and invade the epithelial structure of their fore stomach (less often of the stomach and occasionally of the tongue) causing chronic inflammation and epithelial proliferation culminating in about 60 per cent of cases in the development of a cancer of these structures

[2] Besredka applied this principle in his investigation on the so called Brown Pearce rabbit carcinoma a squamous cell carcinoma readily transplantable from rabbit to rabbit and almost invariably fatal when inoculated into the testicle Besredka demonstrated that the intracutaneous inoculation is totally harmless Moreover the animal in which the malignant tumor has been absorbed acquires a lasting immunity to subsequent inoculations with the cancer irrespective of the organ or *structure utilized*

Recently Kidd (Jour Exper Med 71 335 1940) found the Brown Pearce carcinoma to contain an antigen capable of producing antibodies (see Section *Viruses*)

cancer is prevalent in the male was considered to favor this theory Nicotine, pyridine, phenolic bodies, constitutents of tobacco, were looked upon as "irritating carcinogenic substances" However, these chemicals have never been proven carcinogenic

Studies of lungs of heavy smokers failed to reveal changes in bronchi or pulmonary parenchyma that could be attributed to smoking

Since tar is the only carcinogenic substance which the smoking of tobacco yields, attempts were made to observe its effect on laboratory animals Tobacco tar has, therefore, been applied to the skin and mucosa of mice but no cancers were obtained Flory, by destructive distillation of tobacco, obtained a tar product which he applied (painted) to rabbits The animals developed papillomas but no carcinomas In another series of experiments rabbits were painted with tar obtained by smoking tobacco in pipes Here, too, no carcinomas were produced

Evidence thus far adduced is contrary to the idea that bronchiogenic cancer is caused by tobacco.

RADON EMANATIONS

An etiological relationship between primary carcinoma of the lung and radon emanations was suggested from the observation that a large percentage of miners in the Schneeberg (Germany) and Jáchymov (Czechoslovakia) mines had died of bronchiogenic carcinoma

The observation goes back to the 16th century when it was found that a great number of miners of the two localities suffered from a fatal disease of the lungs which affected them after a long period of work in the mines the worker often became ill years after he had been in retirement The nature of the disease remained obscure until 1879, when the noted pathologist Carl Weigert diagnosed it as a lymphosarcoma However, this diagnosis was revised in 1922 and the conclusion reached that it was a bronchiogenic carcinoma

Investigation revealed that of six to seven hundred miners about 32 died annually, and of these 24, or about 75 per cent, succumbed to bronchial cancer It was further revealed that from 1875 to 1912 two hundred and seventy six miners had died of tumor of the lung, 10 of tuberculosis, and 183 of other pulmonary diseases From 1905 to 1912, fifty nine miners had died of tumor of the lung, 29 of other diseases of the lungs, and 49 of miscellaneous causes (The number of miners in 1912 was 289) Thus the percentage of lung tumors for the years 1905–1912 and 1875–1912, respectively, was 44 and 41 Lange in 1935 found that the percentage of pulmonary cancers among the Schneeberg miners was even higher, from 60 to 70

Jáchymov (Joachimstal) mines about thirty miles from Schneeberg

also have been known for centuries to yield a high mortality among the miners caused by a disease of the lungs As in Schneeberg the symptoms of the malady were chronic cough blood streaked sputum pain in chest *dyspnea and gradual decline culminating in death As in Schneeberg,* the disease often manifested itself years after the miner had begun work in the mines and not infrequently years after his retirement

Despite the short distance between Schneeberg and Jáchymov and despite the similarity between the symptomatology of the diseases in the miners of the two localities respectively the pulmonary condition in the Jáchymov workers remained unknown until 1929 when Lowy identified the first case of a bronchiogenic cancer In the following two years 18 new cases were found in 25 men that came to autopsy Those with cancer had been engaged in the Jáchymov mines from 14 to 23 years A number of them had died from 1 to 27 years (usually six to nine years) after leaving the mines While in Schneeberg the diagnosis up to 1922 was lymphosarcoma in Jáchymov up to 1929 it was tuberculosis

That the pulmonary tumors were etiologically related to the occupation in the mines was apparent from the epidemic dimensions of the disease and indeed from the fact that the population of the same districts not engaged in the mines suffered from bronchial cancer to a lesser degree A *trait proper to occupational cancer in general namely a long incu* bation ' period between the initial engagement in the offending trade and the inauguration of the cancer was likewise characteristic of the *Berg krankheit* (as it was called by the miners) in Schneeberg and Jáchymov That the bronchiogenic carcinoma often developed in miners several years six to nine after their retirement was also typical This too is distinctive of aniline arsenic and x ray cancers

Since the opening of the mines in the 16th century copper iron silver cobalt arsenic bismuth and nickel have been mined In the latter part of the 19th century pitch blende used in the manufacture of uranium dyes was mined especially in Jáchymov In 1909 the manufacture of radium was started in Jáchymov and from that period to 1925 twenty six grams of radium element has been produced Curie obtained radium from pitch blende secured at Jáchymov

The particular agent responsible for the bronchial cancer in the miners has been the subject of multiple investigations with discordant results The opinion however is prevalent that it was radon found in abundance in the mines *Other factors too were suggested* such as pneumoconiosis produced by the dust arsenic and possibly heredity The mines had been operated for hundreds of years and the miners had always lived an isolated and segregated life frequently intermarrying (inbreeding)

The radon it was conjectured acts on the lungs not only through in

halation of radium emanation but also by way of absorption through the skin. That workers engaged in radon industry are liable to develop malignant disease by ingestion, inhalation of the noxious substance and also possibly through other avenues has been demonstrated in the case of workers of the American Luminous Dial Plants where osteogenetic sarcomas were found in seven women 20 to 30 years of age employed in that industry from one to four years. As the workers customarily pointed the brushes containing the luminous points by drawing them between their lips, it was assumed that ingestion of the substance rather than its inhalation was responsible for the inauguration of the malignant disease of the bones.

Why the bones and not other organs were affected has not been fully explained. *In this respect it is of interest to note that the reason for the* scrotal localization of the cancer in the chimney sweepers or of the urinary bladder in aniline workers is not entirely clear, for it is known that in the chimney workers not only the scrotum but the entire body is thickly covered by the soot (concentrated pitch), while in the aniline workers the dye penetrates into the body through inhalation or by absorption of the skin. The kidneys or the ureters have not been known to develop cancer or to be otherwise affected.

In all likelihood there exists a susceptibility *sui generis* of different organs and tissues to malignant disease. This is apparent in the lower animals. Rats, for example, frequently suffer from sarcoma of the liver which arises in the wall of a *taenia* cyst, whereas mice suffering from the same disease rarely develop sarcoma. Also mammary cancer is very frequent in mice *while rats are susceptible to carcinoma of the uterus* but hardly ever develop cancer of the breast.

Whatever the avenue of entry, it seems reasonably certain that radon was responsible for the cancer of the bronchus in the Schneeberg and Jáchymov miners.

Chromium

Of more recent origin is the knowledge of chromium as a cause of bronchiogenic cancer. Chromium and its compounds are used in the production of various alloys, especially *with steel, for electroplating of metal parts*, in the manufacture of chromium pigments, dye mordants, for tanning of hides, aniline dyes, colored crayons, colored paper, colored glass and numerous other objects. Chromium compounds act as a corrosive on the skin and mucous membranes of the upper respiratory tract, and sometimes of the intestinal tract. The most characteristic lesion found in chromium workers consists in ulceration and destruction of the nasal septum.

The first observation of a bronchiogenic cancer in a worker engaged in

the chrome industry was apparently made in 1935 (Pfeil) and similar findings have been recorded since by others Although the number of reported cases is small and observations from countries other than Germany are lacking it seems likely that chromates are an industrial hazard in the genesis of cancer of the lung

As in other industrial cancers the incubation period in chrome-cancer is protracted over a number of years Clinically and pathologically too it differs in no way from bronchial cancer caused by other substances[1]

PNEUMOCONIOSIS

Diseases of the lungs due to dusts silicosis and asbestosis were identified at the end of the past century and as in bronchogenic carcinoma their emergence from obscurity and their rapid rise were due chiefly to the extensive use of radiography

Silicosis When chemically pure silica dust (SiO_2) particles of which do not exceed 10 microns in diameter reach the pulmonary alveoli they provoke a cellular response not unlike that of virulent tubercle bacilli The cells normally found in sparse numbers on and within the walls of the air sacs begin to swell in size and in number detach themselves from their sedentary seat and avidly phagocytose the siliceous particles They often gorge themselves to such an extent that their cytoplasms burst from the load as well as from its toxicity The liberated particles are then picked up by newly arrived voracious macrophages which in their turn either succumb from indigestion or carry their load to hilus lymph nodes They also agglomerate in situ to become transformed into fibroblasts (densely packed macrophages usually undergo such a metamorphosis) ultimately they become hyalinized and calcified A ripe siliceous nodule ordinarily about six microns in diameter is thus made up of concentrically arranged dense fibrous and hyalinized tissue with a calcific center and fibroblasts lymphocytes and carbon pigment at the periphery The firm nodules like minute glass beads are disseminated throughout both pulmonic fields at first in relation to the points of division of the bronchial tree later diffusely In some instances due to superimposed infection or to atelectasis the nodules form massive agglomerations which produce a radiographic shadow imitating bronchogenic carcinoma The damaged parenchyma carries with it changes in the bronchial tree as evidenced by bronchiolitis obliterans and by bronchiectasia but precancerous changes such as metaplasia or excessive proliferation of epithelial cells are rarely observed

Of all the complications of silicosis tuberculosis (silico tuberculosis) is

[1] Block in a recent article suggested commercial lead as a possible inciting factor in bronchogenic cancer

the most redoubtable, being responsible for the majority of deaths among silicotics, 65 to 75 per cent

Case Reports In 1932 I reported a case of a bronchiogenic cancer in a *pneumoconiotic lung in a man of fifty* seven who had been a plasterer for thirty years He entered the hospital complaining of swelling of the abdomen and lower extremities He had been dyspneic for two years and had coughed for several years He was cyanotic with a purplish hue The partoid glands were enlarged and the veins of the neck and abdomen were markedly dilated There was ascitis and clubbing of fingers

Necropsy revealed pneumoconiosis and chronic interstitial pneumonia also, a right bronchiogenic carcinoma of microscopic dimensions The mucosa of many bronchi showed metaplasia

Jasso and Fine studied 21 patients with silicosis, most of whom had died of tuberculosis In one patient, aged 52, a stone cutter for 20 years whose lungs showed no tuberculosis, a bronchiogenic carcinoma was present

Charr analyzed the records of 174 patients with silicosis treated at White Haven Sanatorium Four of the 36 (11 01 per cent) that were examined post mortem presented carcinoma of the bronchus The ages of the patients respectively, were 36, 43, 48 and 50

The study by Klotz was based on 50 cases of silicosis Five of these showed cancer of various organs and four of the bronchi (8 per cent) It is of interest that in the same period of 4 500 necropsies, 808, or 17 7 per cent were carcinomas 53 of which were bronchiogenic (1 17 per cent of all necropsies and 6 5 per cent of all cancers) Klotz believes that silicosis may be a definite predisposing factor in the development of carcinoma of the lung' The ages of his patients were respectively, 45 45, 50 and 54 Their exposure to silica dust varied from 5 to 30 years Three of the carcinomas were anaplastic and one was an epidermoid

In the opinion of Anderson and Diblle "a group of pulmonary cancers exists in which the organs contain an excess of silica and show histological evidence of silicotic fibrosis The role of silicosis is etiological'

Vorwald and Karr compiled reports on the roentgenologic observations of lungs of 57,362 males exposed to occupational dust Evidence suggested primary pulmonary cancer in 3 of them, an incidence of 0 005 per cent Of 1,357 cases studied at the Trudeau Sanatorium at Saranac Lake, but one case of pulmonary tumor was diagnosed Of the 14,230 cases in which silicosis was not present, only two presumptive pulmonary tumors were noted

The statistics based on roentgenologic evidence was supplemented by necropsies from 3 739 cases collected from the available literature and 178 from their own laboratoy There were but thirty two cases in the com

bined series showing primary malignant tumors in the lungs which suggests an average incidence of about 0 8 per cent They reached the conclusion that inhaled dusts cannot be considered as etiologic factors in the development of primary carcinoma of the lung

Kennaway and Kennaway stated that the factors which lead to silicosis appear not to be active in producing cancer of the lung

Asbestosis Asbestosis is another form of pneumoconiosis caused by long continued inhalation of asbestos dust The dust given off from asbestos in the process of manipulation consists of fragments of fibers and small particles of rounded or angular shaped needle like dust particles the needles varying in size from 10 to 120 microns While the smaller particles are readily accommodated in the alveoli the larger ones are lodged in the air sacs and in the terminal bronchioles The remarkable aspect of the reaction to the dust is the formation of curious golden yellow segmented structures asbestos bodies which are probably produced from a substance absorbed by the needles and coagulated as a gel The asbestos bodies are slender elongated segmented structures with bulbous ends assuming a dumbbell or drumstick shape they are present in the sputum as well as in the pulmonary tissue fixed in formaldehyde

The asbestos dust is phagocytosed by macropages to a much lesser degree than silica Unlike silicosis which is characterized by the formation of miliary nodules asbestos is distinguishable by fibrosis about the terminal bronchioles and within the pulmonary parenchyma also by atelectasis and by the formation of bronchiectasis The lungs have a veiled or ground glass appearance which in typical cases is confined to the lower half of the thorax while the upper shows compensatory emphysema complicated occasionally by voluminous bullae which at times rupture inducing spontaneous pneumothorax

Case Reports Holleb and Angrist found asbestosis combined with bronchiogenic carcinoma in two men aged 52 and 58 respectively who had been exposed to asbestos for 25 years In analysing 2 451 necropsies performed in their hospital they found 401 cases (16 36 per cent) with cancer of various organs of which 59 (14 71 per cent) were bronchiogenic The two primary pulmonary cancers were found in patients with asbestosis

In 4 137 necropsies performed at Yale Medical School from 1918 to 1938 Homburger found 45 (1 08 per cent) cancers of the bronchus During the same period asbestosis was diagnosed eight times Of the eight with asbestosis bronchiogenic cancer was found in four instances and of the seventeen with silicosis cancer of the bronchus was discovered in two only The world literature contains only 19 cases (table 11) of the combination of asbestosis with bronchiogenic carcinoma

TABLE 11

AUTHOR	YEAR	SEX	AGE	OCCUPATION IN ASBESTOS INDUSTRY	DURATION OF EXPOSURE	FREEDOM FROM EXPOSURE BEFORE DEATH	NATURE OF TUMOR	PRIMARY SITE	METASTASES
Lynch and Smith	1935	M	57	Weaver	21 years	4 *months*	Squamous cell	Right lower lobe	Same lung
Gloyne	1935	M	35	Spinner	8 years	9 years	Squamous cell	Right lower lobe	Same lung
Gloyne	1935	F	71	Mattress and Opening Department	19 months	15 years	Squamous cell	Right upper lobe	Pleura
Egbert and Geiger	1936	M	41	Weaver	17 years	2 years	Glandular	Left lower lobe	Widespread
Gloyne	1936	M	59	Packer	10½ years	2 months	Oat cell	Left lower lobe	Same lung and pleura
Nordmann	1938	F	35	Spinner	7 years	9 years	Squamous cell	Left lower lobe	Liver and kidney
Nordmann	1938	M	55	Pre spinning assembly	7 years	12 years	Squamous cell	Left lower lobe	Widespread
Lynch and Smith	1939	M	50	Weaver	13 years	3 years	Squamous cell	Right lower lobe	Pleura and mediastinal nodes
Koelsch	1940	No details known							
Linzbach and Wedler	1940	No details known							

Lynch and Weller	1941	M	61		At least 3 years	Not known	Squamous cell	Right lower lobe	None
Holleb and Angrist	1941	M	58	Pipe insulator	25 years	9 weeks	Squamous cell	Right upper lobe	Mediastinal nodes kidney adrenal
Holleb and Angrist	1941	M	58	Pipe insulator	25 years	10 years	Oat cell	Right lower lobe	Widespread
Demeules and associates	1941	M	50	Bagger	20 years	21 month	Alveolar cell	Left lung	Pleura
Demeules and associates	1941	M	57	Machine adjuster	25 years	4 months	Squamous cell	Right lung	Pleura
Homburger	1942	M	45	Not known	5 years	1 year	Squamous cell	Right lung	Diaphragm
Homburger	1942	M	43	Not known	20 years	17 months	Anaplastic	Left lower lobe	Pleura
Homburger	1942	F	41	Not known contact with asbestosis	Not known	Not known	Squamous	Right lung	Liver adrenal stomach hilus lymph nodes

In summary, the opinion of nearly all observers is to the effect that silicosis plays no role in the genesis of bronchiogenic carcinoma The number of cases of asbestosis combined with bronchiogenic cancer is too small to enable one to draw conclusions However, the data suggest that asbestosis is probably carcinogenetic

Influenza

Although influenza has been the source of extensive studies, the micro organism which causes it has not been definitely indentified The changes in the lungs caused by the supposed pathogen have never been fully de scribed Generally injuries varying in severity are inflicted on the smaller bronchi necrosis of a part or of the entire bronchial wall is most con spicuous There often occurs a peribronchial pneumonia and hemor rhages In the larger bronchi the normal columnar epithelium is fre quently replaced by stratified squamous epithelium or there occurred a metaplasia (protoplasia) of the bronchial mucosa

Winternitz in addition to metaplasia found

In many cases (he does not indicate the number) epithelial proliferation invasion of the surrounding pulmonary tissue and a typical histological picture of an infiltrating malignant epithelial neoplasm

Cancer of the lungs as emphasized elsewhere in this treatise is bronchio genic The disease in these organs results from an excessive (pathologic) regeneration of the basal cells of the bronchial mucosa In a number of instances the regeneration results in the formation of a layer of stratified squamous epithelium protoplasia of the bronchial mucosa Since in other viscera this particular type of regeneration has been observed to end in the formation of a cancer in about 30 per cent of cases it was pre sumed by some observers that the same pathologic phenomenon would likewise hold true for the lungs These observers have therefore expressed the belief that the alleged increase in pulmonary cancer results from the epidemic of influenza of the year 1918–1919

However those who have investigated clinical material found that a very small number of their patients had had influenza or influenzal pneumonia prior to the pulmonary malignant condition Thus Kikuth by investigating the records of 249 patients that came to necropsy from 1889 to 1923 found a history of influenza preceding the bronchiogenic cancer only in 21 cases Staehelin found that of 67 cases of primary cancer of the lungs 17 had occurred since the middle of 1918 and of these only 4 gave a history of influenza preceding the malignant condition Simpson s material reveals that only 5 in 139 cases had developed a bron chiogenic cancer following an attack of influenza In the author's material only a few patients gave a history of influenza during the epidemic

There is also disagreement as to whether the alleged increase in this malignant disease began in the period following the epidemic of influenza. In 1912 Adler and other writers of the last two decades of the nineteenth century stated that primary carcinoma of the lung is probably not of rare occurrence but that the disease is overlooked or not reported. In more recent years Staehelin noted that in his experience the climax was reached in 1912, 1913 and 1914. In Seyfarth's report on 307 patients pulmonary neoplasms occurred in 11.23 per cent of all cases in the period between 1914 and 1918 and 8.75 per cent between 1919 and 1925.

It is questionable whether an "acute" irritating agent such as the etiologic agent of influenza can initiate a cancer. The opinion is prevalent that only a protracted application of an irritating agent will provoke a *malignant tumor. Literature contains few reports where the authors* claimed that a malignant epithelial process had been inaugurated by a single application of an irritant. Stauffer observed the appearance of an ulcus rodens on the cheek of a sixty-six-year-old foundry worker thirty days after he had sustained a burn. The patient had had, however, hyperkeratosis and a "precancerous" condition of the skin for a number of years prior to this accident. Stauffer is of the opinion that in instances where a cutaneous cancer rapidly follows a single application of a traumatizing agent, the part of the skin in the vicinity of the cancer which has not been *subjected to trauma should be investigated, for it is possible* that the trauma has merely accelerated an already existing pathologic (precancerous) process.

Indeed, the fact that the *antecancerous* bronchial metaplasia has been found at necropsy following cases of influenza would merely indicate that this pathologic process is encountered in a certain percentage of cases of influenzal pneumonia ending in death. But metaplasia of the bronchial epithelium was also observed in fatal whooping cough, measles, diphtheria, and also in instances of noninfluenzal pneumonia. There are, however, very few reports to the effect that individuals who had recovered from these diseases subsequently suffered from grave bronchial disturbances such as metaplasia of the bronchial mucosa. Similarly, no demonstrable bronchial sequelae have ever been noted at necropsy in patients with a history of influenzal pneumonia or pertussis who subsequently died of other causes.

The conception, therefore, that the alleged increase in bronchiogenic cancer is a sequel to influenza cannot be relied upon.

Viruses

Virus Tumors. A tumor is considered of viral origin when it can be transmitted from animal to animal by a cell-free filtrate or inoculation is followed by the formation of specific antibodies.

The idea that a neoplastic disease may be inaugurated by a virus dates back to the past century but evidence was lacking until Rous in 1910 succeeded in transmitting a tumor (sarcoma) from one chicken to another by *a cell free filtrate which was believed to harbor the inciting virus*. In recent years Rous and his associates have been able to induce cancer in rabbits by injecting acellular solutions obtained by filtrating tumor tissue through cell tight filters, the filtrate presumably containing the virus.

In 1931 Shope found in the Middle west a large number of wild cotton tail rabbits affected by small multiple papillary fibromata. The apparently benign tumors were transmitted to the wild cottontail rabbit as well as to the domesticated rabbit by inoculating them with tumor tissue (grafts) or with filtrates devoid of cells. It was significant that while the papilloma in the wild animal generally pursued a benign course it became cancerous in the domesticated rabbit in a large number of cases. *The animal bearer of the tumor developed specific antibodies* which increased with the advance of the growth and which protected healthy rabbits against inoculation. Similar to viruses, the causative factor possessed an affinity for certain cells (cytotropism) such as the epidermis causing an epidermoid carcinoma of the skin.

Recently an epithelioma of the rabbit (so called Brown Pearce epithelioma named after the pathologists who first described it) which could be transmitted from animal to animal by grafts only (not by cell free filtrates) was found to manufacture antibodies which increased in amount with the advance of the tumor. The pathologist Luké ascertained that a carcinoma of the kidney which he found in the swamp frog was caused by a virus. A variety of tumors and leukemias in fowl have been demonstrated to be caused by viruses.

The "Milk Factor". Experimental oncologists have noticed that some strains of mice are particularly prone to develop cancer of the mammary gland in advanced age while others develop the disease very rarely. By interbreeding the two strains it was found that the tendency to transmit *the disease came from the mother's side. A startling observation* was made that if newborn females from a high cancer strain are suckled by a foster mother from a low cancer strain they will go through life without acquiring the malignant disease of the mammary gland. On the other hand, newborn females from a low cancer strain suckled by a foster mother from the high cancer strain will develop mammary cancer. Studies of this phenomenon revealed that (1) The cancer producing agent *is present* in the milk of the high cancer strain. (2) It is transmitted by the mothers indemn from mammary cancer, (3) Cancer develops when the mouse has reached adult age and its mammary gland becomes mature. (4) The young mice of the low cancer strain who suckled in the "milk factor

from their high cancer strain foster mothers, transmit it in their turn to their offspring generation after generation

It was assumed that from the intestinal tract of the suckling the "factor" passes into the circulation and thence into the mammary gland where it is stored until the advent of hormonal activity The "factor" passes through a bacteria tight filter and displays characteristics proper to viruses

Viruses and Hormones Viruses and Tarring The role of folliculin in the production of carcinoma of the breast in female mice has been demonstrated by many observers This became apparent from the observation that mice from a strain highly susceptible to cancer of the breast remained free from the disease if their ovaries were removed before the age of four months while their mates of the same strain with ovaries intact developed cancer of the gland It was discovered that the estrogenic hormone acted with greater promptness on mice liable to develop mammary cancer spontaneously, while the naturally refractory strains resisted the estrogen Even the male of the cancer sensitive strain, usually immune to cancer of the breast, developed cancer of the gland when treated with the follicular hormone

It was ascertained that in the induction of cancer of the breast in mice bearers of the milk factor" *estrogen is a conditio sine qua non* The malignant disease will not develop until the rodent has reached the period of hormonal activity, moreover the progress of the growth can be accelerated by increasing the amount of hormone

The role of a virus in experimental tar cancer was also stressed in recent years As stated in the early paragraphs of this chapter the repeated application (painting) of tar to the skin of rabbits leads to excessive proliferation of the epidermis forming papillary outgrowths which either develop into cancer or disappear (heal) if the tarring has been discontinued However, if the animal is infected with a virus (isolated from the papilloma of Shope) it usually concentrates in the area painted with tar and the arrested and innocuous papillary growth almost abruptly assumes a malignant course and soon appears as a squamous cell carcinoma

These observations (and many of a similar nature which cannot be adequately summarized in this space) have given great prominence to the idea that viruses play an outstanding role in carcinogenesis Indeed many observers hold the view that viruses are the single factor causing carcinoma They believe that man probably contracts or harbors carcinogenic viruses which act in cooperation' with hormones, chemical and physical agents parasites and nematodes respectively Rous, one of the most brilliant exponents of the virus theory of cancer believes viruses to be 'the nearer cause of cancer the only carcinogenic agent known to produce tumors by *direct* action for other carcinogenic substances act

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At necropsy a primary carcinoma was found in the upper lobe of the left lung, metastatic to the mediastinal, supraclavicular, periaortic lymph nodes, right adrenal and both kidneys

The authors considered that their case presented as nearly completely satisfactory evidence as one can hope to secure of the development of primary carcinoma of the lung as a direct result of a single traumatism to the lung tissue ' They added, however

Of course, it is not possible to say there was not already a carcinoma, too small to be detected in the roentgen ray film, growing in the part of the lung that was traumatized at the time of the injury But in view of extreme infrequency of primary carcinoma of the lung arising in the periphery of the upper lobe, to support such an explanation of this particular case requires a stretching of 'the long arm of coincidence' to the vanishing point '

Indeed, the usual negative roentgenologic finding has a limited value I have observed several cases where careful roentgenologic examination showed no abnormalities in the lungs in the presence of a cerebral metastases from a carcinoma of the bronchus One patient with atypical signs of an intracranial lesion of about four months duration, had been investigated by a competent roentgenologist for the presence of an intrathoracic neoplasm but the lungs were found to be "clear " The necropsy however, performed a few days later, revealed a small bronchiogenic carcinoma with metastases

The opinion is prevalent that only a protracted application of an irritating agent will provoke a malignant tumor It has been observed that there occurs a long interval (pause) between the application of the irritating substance and the inauguration of cancer Again, the statement made by Wells and Cannon that primary carcinoma of the lung arising at the periphery of the upper lobe is "extremely infrequent" has not been corroborated in recent years

The author is very skeptical of any etiologic relationship between single traumatic insult and cancer of the bronchus[5]

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[5] Some observers claim that trauma may exert a concurrent action (effect) on the formation of tumors without participating in the primary process

indirectly by inducing a preliminary chronic inflammation (irritation) which only ultimately undergoes a malignant metamorphosis"[4]

CONCLUDING NOTE

While in lower animals some spontaneous malignant tumors have been convincingly shown to be caused by viruses, in man no instances have as yet been observed None of the traits characteristic of virus carcinoma has ever been noted in bronchiogenic cancer

Trauma

The etiologic relationship between trauma and bronchiogenic cancer may be considered briefly here

It has been observed that trauma of an external organ or structure is followed by the development of a benign or malignant growth in the traumatized area However, an etiologic relationship between trauma and cancer of an internal organ has never been satisfactorily explained It is obvious that in instances when a malignant disease of an internal organ has closely followed a traumatic accident the possibility of the trauma being merely accidental and superimposed upon an inapparent tumor or a cancer in the preinvasive stage cannot be excluded

Wells and Cannon described an instance in which a bronchiogenic cancer appeared following a trauma of the thorax

A man, aged sixty, in general good health, was knocked down by an automobile on September 1, 1926 He suffered severe pain in the chest and was taken to a hospital where a roentgen ray examination performed the next day revealed fracture of the left third, fourth and fifth ribs in the midaxillary line There was also distinct evidence of traumatic injury to the lung, namely, hemoptysis and subcutaneous emphysema extending over the entire body The roentgen films showed no evidence of any neoplasm in the lung The fracture healed uneventfully, and the patient seemed to be in good health until the following August, when he complained of pain in the left side of the chest He developed a cough, and symptoms suggestive of pulmonary tuberculosis appeared, but no tubercle bacilli were found in many specimens of sputum Repeated bronchoscopic examinations failed to reveal a bronchial growth, but roentgen films disclosed cancer in the left upper lobe with metastases to the hilus lymph nodes Death occurred on August 17, 1928, two years after the injury to the lung and one year after the onset of symptoms

[4] The possibility that in Fibiger's experiments the cancer induced in the rats was caused not by the nemathode of the cockroach but by a virus which it harbors was conjectured The experiments could not be repeated by Fibiger and others with cockroaches obtained from other sources

ETIOLOGY

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Chapter IV

METASTASES

Spread From the mucosa of the bronchus the cancer spreads within and around the bronchial wall, toward the pulmonary parenchyma, distant organs and occasionally toward the trachea and esophagus inducing dyspnea and dysphagia (fig 33) The neoplastic cells advance in broad sheets pushing and destroying the lung, or penetrating the pulmonary tissue in narrow columns They produce a fibrous stroma which often leads to their own imprisonment and slows their advance The fibrous stroma is much pronounced in squamous cell cancer, less in oat cell cancers and least in round cell and adeno carcinoma types The cartilagenous plates of the wall of the bronchi never impede the progress of the tumor The malignant cells usually by pass, surround and occasionally invade them (fig 34) Some tumors form bulky masses around the bronchus compressing and narowing their lumen (fig 35) The notion of older pathologists that this type of cancer originates from the cells of the bronchial mucous glands has not been corroborated by recent observers

The problem of the dissemination of a malignant tumor with the formation of distant metastases is of major importance from the prognostic and therapeutic points of view In the study of the subject one must consider

1 The propensity of the tumor to spread to distant organs
2 The route used by the neoplastic cells to reach remote organs
3 The predilection of metastases for certain organs
4 The clinical manifestations
5 The management

Factors Involved The intimate mechanism of metastasis is not understood although many observers have investigated the question experimentally Cohnheim was the first to stress that it depends largely on the host or systemic factors the nature of which he did not explain This theory was suggested by observation that metastatic deposits thrive in some organs and perish in others In bronchiogenic cancer the liver is involved in about 40 per cent of cases, the contralateral lung in about 30 per cent the heart muscle and the spleen, respectively, in only 9 per cent

The size of the primary tumor seems to play a role, for small tumors often yield widespread metastases Small testicular neoplasms produce voluminous metastases in the abdominal lymph nodes, and minute gastric,

renal, bronchiogenic and prostatic cancers not infrequently provide extensive and multiple metastases Geschickter and Copeland noticed that



Fig 33 Squamous cell carcinoma of the bronchus to the left upper lobe in a man of 66 The tumor permeated the tracheal wall leading to marked narrowing of the lumen invaded the mediastinal space mediastinal lymph nodes and esophagus compressed the superior vena cava left pulmonary artery and vein and produced a left hemothorax

small asymptomatic hypernephromas often give rise to widespread skeletal metastases, whereas large cancers of the kidney are less apt to metastasize extensively This phenomenon was interpreted by Ehrlich on the basis of his Athreptic theory

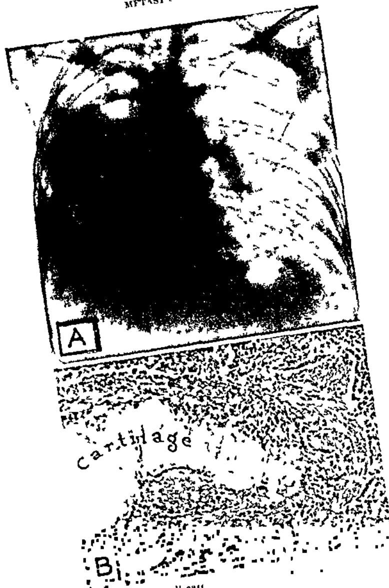
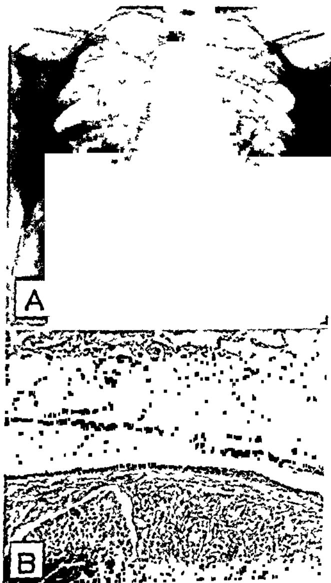


Fig. 31. A squamous cell carc... invading the bronchial cartilage ... B tumor

Ehrlich observed that a cancer transplanted from a mouse to a rat continued to grow in the new host for about seven days after which it began to regress until it finally healed But the same tumor retransplanted



in the early stages of its regression to a healthy mouse regained its former proliferative activity. The experiments are known as Cross Experiments (Zick-Zack Versuche). The failure of the tumor to thrive in the new host

was attributed by Ehrlich to the lack of specific nourishing substances. Large tumors (conjectured Ehrlich) attract the bulk of the specific nourishment for themselves leaving "crumbs" only for the daughter tumors (metastases) thus starving them out of existence. On the contrary, small tumors consume little food leaving ample nourishment for the offspring.

On the same basis attempts have been made to explain the observation that the surgical removal of a tumor is not infrequently followed by the prompt appearance of distant metastases. While some observers attributed the postoperative spread to "careless" handling of the tumor by the surgeon, others attributed it to a biologic phenomenon, the Athreptic theory of Ehrlich.*

Observations have also been made that soft, cellular tumors metastasize more readily than those which are poor in cells and hard in consistency. It also was noticed that in the aged, cancer is much less apt to metastasize than in younger persons. It seemed that dissemination of cancer is often in inverse proportion to the rate of its growth. (It is possible that rapidly growing cancers cause death before widespread metastases have time to develop.)

While a systemic influence can only be surmised, the accessibility to cancer cells is of indubitable significance. In the rabbit, for instance, Brown and Pearce noticed that the frequency of metastases diminishes with the distance from the central axis of the body. Analysis of the different organs to which cancer of the bronchus metastasizes reveals that this holds true in the human as well. In only rare instances were metastases found in the abdominal viscera below the region of the kidney, while the brain, liver and adrenals were common seats for secondary deposits.

Prostatic metastases seem to bear a dependable relation to the proximity of the primary tumor, i.e., the nearer the primary, the higher the incidence of bone involvement (Turner and Jaffe).

Some investigators noted similarities between neoplastic and bacterial metastases, both respectively selecting tissues suitable for their nutritive needs.

Lymphatic Spread. Observers of the past held that carcinoma disseminates essentially by way of the lymphatics while sarcoma propagates via the blood stream. At present it is conceded that malignant epithelial tumors metastasize by various channels.

When neoplastic cells gain entry into the lymphatics, which are usually the first to be invaded, they permeate their lumens using them as channels for the transportation of cancer cells to tributary lymph nodes, blood

* Tyzzer observed that following the partial excision of an implanted tumor in the mouse metastases appeared and assumed rapid growth.

vessels and remote organs Embolization is the essential mode of metastasis, while permeation occurs in rare instances When it happens the tumor cells grow within the lumen of the lymphatic vessel "conquering new territory" step by step Their driving force is an internal pressure resulting from their own proliferation As a rule they follow the current of the lymph ("othograde infection") "Cancer thus spreads" wrote Handley, "by permeating the lymphatic system like an invisible annular ringworm" When the lumen of the lymphatic is blocked by fibrosis or outside pressure cancer cells continue their proliferation against the lymph stream ("retrograde infection")

Lymphangitis Carcinomatosa The lymphatics of the lungs and pleura may be permeated by cancer which originated in the lung or stomach The gastric cancer passes from the stomach to the perigastric lymph nodes to the tracheal and the mediastinal nodes and produce stasis in the lymphatic circulation of the lungs and a retrograde spread of the tumor There occurrs nearly complete obliteration of the lymphatic vessels by tumor accompanied by a neoplastic endophlebitis The primary gastric cancer in these cases often remains asymptomatic the complaints of the patient refer chiefly to the cardio-respiratory organs The patients develop failure of the right heart to which they succumb When bronchiogenic cancer permeates the pulmonary lymphatics it is usually unilateral and symptoms of right heart failure are lacking

Illustrative Case

Case 1 History In 1926 a leather operator, aged 25 experienced a sudden violent and uncontrollable hiccough Roentgenologic examination of the chest revealed a mass at the base of the right lung (fig 36) As periodic examinations during the next four years showed no change in the mass and the patient's condition remained unchanged the diagnosis of benign tumor was made One year later, in 1931, the patient complained of pain in the left side of the head, and in July, 1932, non projectile vomiting occurred after meals Cough productive of small amounts of sputum began to trouble him in September, 1932 and soon his strength began to decline He was hospitalized

Roentgen ray examination of the chest showed a mottled infiltration of the entire right lung and a few metastatic nodules in the left lung (fig 37 A) The diagnosis was Bronchiogenic carcinoma with extension by way of the lymphatics

At necropsy the surface of the right pleura was covered with slightly raised grayish streaks and grayish yellow plaques The lung was indurated and on palpation gave the impression of being filled with very fine beads To be sectioned the lung had to be decalcified

Microscopically the tumor was a stratified squamous cell carcinoma embedded in dense connective and hyalin tissue (fig 37 C) The tumor cells permeated the peribronchial and perivascular lymphatics, compressing the lumens of blood vessels and reducing them to mere slits The walls of the larger vessels showed invasion by tumor which also lined the intima

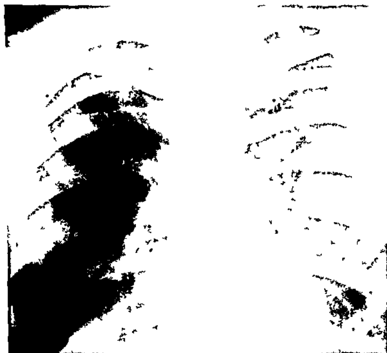


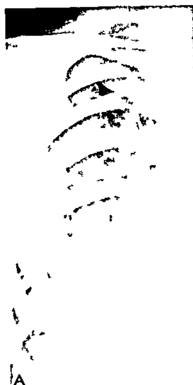
Fig 36 (Case 1) A well circumscribed tumor at the base of the right lung

of the larger veins Of interest was the presence of concentric hyalin and calcific gobules resembling psammoma bodies (fig 37 B and C)

Comment The tumor which originated in a bronchiole to the right lower lobe caused only hiccough at the onset Since the patient was young and the tumor well circumscribed the idea was entertained that the neoplasm was benign Indeed it remained asymptomatic for almost four years It permeated the entire lymphatic system of the right lung causing a remarkable fibrocalcific reaction which imprisoned and destroyed a good portion of the cancer However, it ultimately penetrated the blood

stream and set up metastases in the contralateral lung and possibly in the brain. The illness lasted about seven years after the first symptoms appeared.

Hematogenous Spread. The notion that there exists a type of "lymphophilic" cancer which remains within the lymphatics for life, shunning





entirely the blood stream, is now abandoned; even in the seemingly pure cases of lymphangitic cancer the blood vessels are not spared.

Blood vessels in the vicinity of carcinoma undergo early pathologic changes. This is more marked in veins, which show degenerative changes at the beginning of the disease, while the arteries resist damage for a longer period, and as in inflammatory conditions of bacterial origin they temporarily play the role of "insulators." Neoplastic cells aggressively invade the vascular coat and disseminate throughout the vessel wall by

way of the vasa vasorum (fig 38) This is apparent from the fact that in the arteries where nutrient vessels are prominent in the outer coat, the tumor is essentially periarterial, while in the thin walled veins the cancer is an endophlebitis (fig 39)

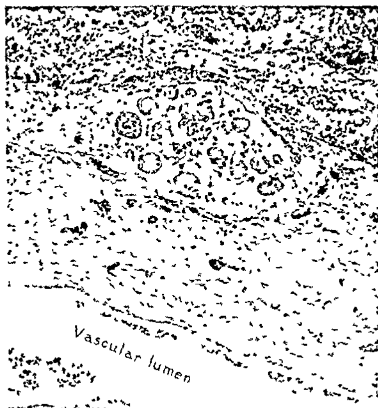


Fig 38 Tumor cells in a markedly dilated nutrient vessel in the pulmonary artery

Hematogenous metastases (figs 40 and 41) occur through the transmission of single cells or minute clumps of cells in the form of emboli Neoplastic cells cross the vascular wall and settle in the surrounding tissue occasionally they grow within the vascular lumen

Types of Metastatic Spread It is desirable to distinguish three main types of metastatic dissemination

1 The *Vena Cava* type for extra pulmonary and extra intestinal cancers
2 The *Vena Porta* type for intestinal cancers

3 The *Pulmonary Artery* type, for bronchiogenic cancer.

In studies on cadavers and live monkeys, Batson, by injecting opaque material into superficial veins, observed that metastasis is effected through a system of valveless vertebral veins which have free and rich anastomoses at each spinal segment with the veins of the thoraco-abdominal cavity (fig 42) According to this author, with every compression of the trunk, the intratruncal pressure is raised to a sufficient height, so that blood flows not into the inferior vena cava but into the vertebral system of veins,



Fig 39 Endophlebitis carcinomatosa Tumor cells in a large pulmonary vein

carrying with it neoplastic cells (or bacteria) Batson found that these intercommunicating veins are physiologically the site of frequent reversals of flow, creating a pathway up and down the spine which does not involve the heart or lungs As the pathway has many connections it provides a ready vehicle for the occurrence of "unorthodox" metastatic patterns It also explains the lack of pulmonary metastases in instances where other visceral organs show their presence

In a study of cerebral metastases from carcinoma of the breast, Hassin ascertained that the tumor reached the brain in the following manner from the periphery tumor cells entered the lymphatics of the neck, then

via the tissue spaces, they penetrated into the perineural spaces, "climbing" upstream to the meninges, and invading the cerebral hemispheres.

There is general agreement that cancer metastasizes to distant organs in various ways. Letulle and Jacqulin stated that in some instances bronchiogenic cancer was transmitted from one lung to the other by way of the bronchi by "spilling" over of cancer cells which implanted (grafted)

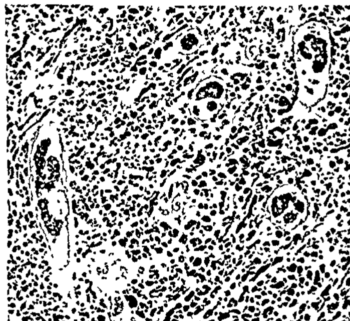


Fig. 40. Cancer cells in the coronary circulation

themselves in the contralateral lung. They defined this type of metastasis as "aerogenous" ("métastase aérienne"). Goldmann observed transmission of mammary cancer by way of the lactiferous ducts.

As already stated, the passage of cancer cells from the lung to the brain is in all likelihood effected through the blood stream.

Distribution of Metastases. Metastases from primary carcinoma of the lung are frequently multiple and their distribution is wide (table 12). In 2,579 cases collected from the literature Ochsner and DeBakey found metastases to the regional lymph nodes in 75.9 per cent, liver 34.4, bones 20.4, adrenals 17.6, kidneys 10.6, brain 14.6, heart and pericardium 10.0, pancreas 5.4 per cent. Frissell and Knox found the lymph nodes invaded in 97.4 per cent of cases. Jaffe failed to find metastases in only

two of one hundred cases The presence of metastases and their incidence is often in direct proportion to the zeal of the pathologist and the time at his disposal

The abundance of metastases in primary carcinoma of the lungs has been attributed to two factors

1 The rich network of blood and lymph vessels of the lungs (Pulmonary Artery type of metastases)

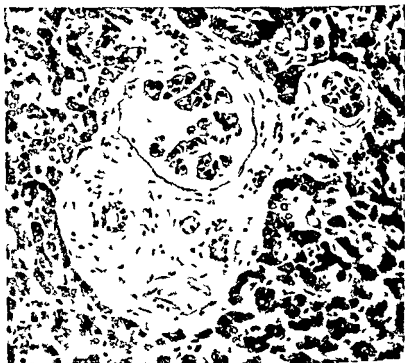


FIG 41 Cancer cells in the hepatic veins

2 The high degree of malignancy of pulmonary tumors

The role of the circulatory apparatus in the dissemination and localization of metastases has been discussed above The statement that bronchial cancer is a highly malignant tumor (more than cancer of other organs) is not born out on close scrutiny This cancer reveals no peculiarities not encountered in other cancers and viewed from this angle it should be regarded as a part of the entire problem of malignant disease However, it is well to point out that bronchiogenic cancer is particularly apt to metastasize to the brain bones and adrenals

Cerebral Metastases The frequency of metastases to the brain and bones was noted in 1925 I wrote "The bones and the brain are apparently

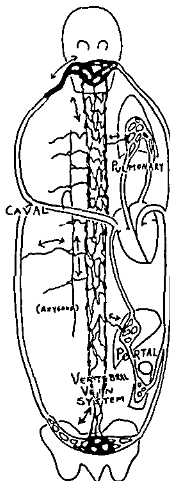


FIG 42 Schematic drawing of the system of vertebral veins (Batson O V The function of vertebral veins and their rôle in the spread of metastases Ann Surg 112 138, 1940)

much more frequently involved by carcinoma of the bronchus than is generally recognized" Of 47 cases reported in 1932, sixteen, or 34 per cent showed secondary deposits in the central nervous system

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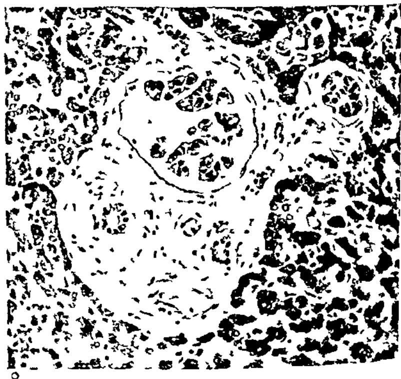


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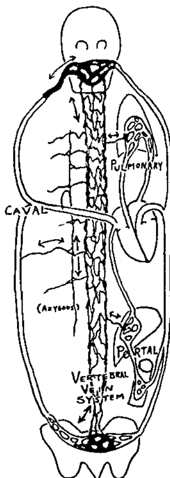


FIG 42 Schematic drawing of the system of vertebral veins (Batson O V The function of vertebral veins and their rôle in the spread of metastases Ann Surg 112 138 1940)

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Ilkington in a study of 72 cases, found that 33 3 per cent of cerebral metastases came from bronchial cancers Grant found 13 5 per cent in 139 cases Globus and Meltzer found that 19, or 57 5 per cent of 33 cases were of bronchial origin Olson found 36 3 per cent, Arkin and Wagner

TABLE 12

Distribution of Metastases from Primary Carcinoma of the Lung[7]

ORGAN	PER CENT	ORGAN	PER CENT
Lymph nodes	81 00	Pancreas	6 35
Liver	40 06	Thyroid	3 18
Adrenals	38 00	Intestines	3 18
Bones	40 04	Subcutaneous tissue	2 40
Contralateral lung	28 08	Stomach	2 20
Kidneys	20 03	Ovaries	2 10
Brain	11 01	Scalp and skull	2 40
Heart and pericardium	9 03	Finger	0 80
Spleen	7 90	Gall bladder	0 80

TABLE 13

Cerebral Metastases from Cancer of Visceral Organs

ORGAN	AUTHOR AND NUMBER OF CASES		
	Baker 114 cases	Hare and Schwartz 100 cases	Globus and Meltzer 33 cases
Bronchus	24	42	19
Breast	24	23	
Stomach	4	3	1
Intestines	3	5	5
Kidneys	9	2	1
Adrenals	6	2	1
Thyroid	1	2	4
Uterus	5	1	
Ovaries	1	1	
Prostate	1	1	1
Unknown	1	16	1

22 per cent King and Ford 19 per cent, Baker 21 per cent, and Hare and Schwartz 42 per cent

Of 319 cases of primary carcinoma of the lung studied postmortem at the Montefiore Hospital 11 01 per cent showed metastases to the central nervous system The discrepancy between the figures emanating from neuro surgical and medical clinics, respectively, is due to the fact that in the latter, brains are rarely investigated postmortem, while the material

[7] The larynx urinary bladder and parathyroids respectively were invaded by cancer in only one instance

collected in neuro surgical clinics is obviously selective However, it is evident that the lungs are the source par excellence for metastases to the brain

The frequent occurrence of cerebral metastases in bronchiogenic cancer is due primarily to the accessibility of the brain there is no barrier between the lungs and the cerebral hemispheres A small embolus from a bronchiogenic cancer may pass from the pulmonary vein and heart directly into the general and then into the cerebral circulation, where it may settle in a site favorable for its proliferation A similar embolus from elsewhere in the body, on its way to the central nervous system, passes primarily through a "sieve" of the lungs, where it is frequently retained and destroyed

It is of interest to note that an abscess of the lung is more frequently complicated by a metastatic abscess to the brain than an abscess from any other visceral organ This is due to the same underlying factor, hematogenous transmission to the brain of a "pus embolus" analogous to the transmission of a carcinomatous cell embolus "

Skeletal Metastases Similar to the brain the bones are reached by cancer cells via the blood stream That the bone marrow possesses no lymphatics was demonstrated for the first time by V Recklinghausen Piney, in recent investigations injected the periosteal lymphatics and observed that the material passed from these structures through the bone and into the endosteal channels He could not force the mass into the bone marrow

Within the red bone marrow the blood vessels break up into many wide and tortuous thin walled channels causing a marked slowing of the blood stream Tumor cells which have gained entrance to the blood stream settle in the sluggish circulation in the center of the bones (within the marrow cavities) wherefrom they reach the periphery

There is probably no cancer (with the possible exception of the laryngeal) that does not metastasize to the bone It is remarkable, however, that cancer of some organs invade the skeleton with remarkable frequency, while others are rarely found in the bones This phenomenon is in accord with the contention that formation of distant metastases depends on systemic factors It is possible that the medium of the bone marrow is favorable for the growth of one type of cancer (mammary prostatic, renal, bronchiogenic) only

The incidence of skeletal metastases from organs *other* than the lungs is shown in table 14

Most authors point out that the statistical incidence of metastases to bones would have been still higher if special studies had been made

The study of Hubeny and Mass at the Cook County Hospital, Chicago, showed a considerable increase over previous years, due obviously to a

more careful search The spine and pelvis were found to be the sites of choice for the secondary deposits, followed by the ribs and the skull

Freid's figures on the incidence of metastases to the bones from the prostate, kidney and bladder are above those given by other observers (table 14) He found that renal cancer (hypernephroma) invades the axial and trunk bones more frequently than the bones of the limbs In

TABLE 14

Skeletal Metastases from Organs Other than Lungs

ORGAN	HUBENY AND MASS	TURNER AND JAFFE	SUTHERLAND	COPELAND	YORT	STEIN	FREID	MULLER
Breast	35 0	57 01	38 0	30 0	36 0			
Prostate	21 0	57 8	40 0	40 0	16 0		58 0	
Kidney	21 2	20 0	5 0	6 0	2 0		45 0	
Thyroid	42 8	37 5	2 0	2 0	1 0			
Uterus	13 6		2 0	1 0	4 0			
Pancreas	4 3	6 3				3 57		21 5
Cervix	2 5	8 0						
Ovary	2 5	6 0						
Bladder	17 5	13 0					10 0	
Bile ducts	40 6							
Esophagus	8 4	1 8				2 94		
Colon			1 0	1 0	2 0	0 93		6 93
Rectum	0 62					5 93		10 52
Small intestines						8 33		2 52
Stomach	1 2	7 4	2 0	2 0	1 0	2 65		
Gall bladder						16 66		3 57
Testes	25 0	20 0						
Tonsils								
Skin								
Nasopharynx	20 0	35 5						20 0
Liver	11 5							20 0
Tonsils								
Tongue lips	4 8	5 2						
Large bowel		11 1						

43 per cent the m[illegible] ngle area of the bone while the primary [illegible] in bronchiogenic cancer was stressed by me in earlier publications

That cancer of the prostate metastasizes to the bones par excellence is widely known It is remarkable that cancer of the urinary bladder metastasizes to bones in only a small percentage of cases In just one of Freid's cases was there a true metastasis, in other cases the skeleton was

involved by direct extension Hubeny and Mass found metastases in 17 5 per cent

The frequent occurrence of skeletal metastases in bronchiogenic cancer has been stressed in previous publications I stated

"The bones, too are apparently frequently involved judging from the clinical and roentgenological pictures Histologic examination of the skeleton was however rarely performed In one instance, at the post mortem examination, the long bones were infiltrated with cancer cells without previous clinical manifestations and without outward changes It is possible that a systematic investigation of bones for secondary tumors would furnish much higher figures than have been recorded "

TABLE 15

Skeletal Metastases from Bronchiogenic Cancer

AUTHOR	PER CENT
Arkin and Wagner	28 0
Fried	40 8
Koletsky	19 0
Mattick	29 0
Rosedale and McKay	32 0
Stein and Joslin	15 0
Jaffe	22 0

I called attention to the fact that often the metastases in the bones are not visible with the roentgen rays

Very few studies were devoted to skeletal metastases from cancer of the lung This was probably due to difficulties encountered in their search Then too the clinician as well as the pathologist examines the bones only when there are specific complaints referred to these structures Usually few bones are examined The discrepancy in the figures given by various authors is apparently due to the methods of roentgenologic and postmortem investigation

My material revealed that according to postmortem findings the bones are invaded by bronchiogenic cancer in 40 per cent of cases A thorough search would very likely increase their incidence The bones the liver and the adrenals were about equally involved The incidence of skeletal metastases from bronchiogenic cancer is shown in table 15

Since the entire skeleton was never investigated it is hazardous to estimate the predilection of metastases for certain bones However, it

would appear that the spine, ribs and long bones in the order named are the most frequently affected

Suprarenal Metastases Unlike the bones which are the site of metastases from cancer of almost every organ, the suprarenals are rarely invaded by extrapulmonary cancers They are the site of choice for metastases from cancer of the bronchus Statistically the adrenals occupy the third place (38 per cent) in the incidence of metastases from primary carcinoma of the lung (table 12) It is difficult to understand why the adrenals should be invaded by metastases more often than the kidneys (20 per cent) or the pancreas (5 83 per cent), unless one accepts the view that a systemic factor is involved Rouvière claims that there is a direct connection between the lungs and the suprarenals Whether the frequency of metastases to these organs is favored by their accessibility to tumor cells or by a systemic factor (favorable soil for their proliferation) cannot be ascertained

Metastases to Lungs In another section the statement was made that the lungs are the point of convergence of the body so that soluble as well as particulate matter that happened to enter the circulation invariably reaches them

Since virtually every visceral cancer penetrates into the blood stream cancer cells necessarily reach the pulmonary circulation In fact studies have revealed the quasiconstant presence of tumor cells in the pulmonary capillaries It was noticed however, that the neoplastic emboli are retained in the meshes of the lungs where they remain immured and are frequently destroyed Due apparently to this phenomenon metastatic deposits are not always found in the lungs In an investigation of 1365 cases by Hubeny and Mass approximately 74 per cent showed skeletal and pulmonary metastases at the postmortem examination Farrel in a study of 78 necropsies found that the lungs were the site of metastases from the breast in 14 4 per cent and urinary organs in 14 per cent Of 7 cancers that arose in the male generative organs the 6 found in the lung came from the prostate It is of interest to note that of the cancers that invaded the lungs (34 per cent) from the gastro intestinal tract none had origin distant to the duodenum Cancers of the rectum sigmoid and descending colon showed no metastases in the lungs From table 14 it will be seen that these cancers metastasize to the bones

Freid found metastases to the lungs from the prostate in 43 per cent of cases from the kidneys in 54 per cent and from the bladder in 7 per cent

Turner and Jaffe found metastases in the lungs from the prostate in 28 4 per cent, from the kidneys in 40 per cent and from the bladder in 19 5 per cent

In a study of 100 cases Jaffe found that bronchiogenic cancer metastasized to the contralateral lung in 43 per cent My observation is that such *metastases occur in 30 per cent* [a]

METASTASES TO BRONCHI

Until recent years the notion was entertained that the bronchus which is the site of origin of the tumor is hardly ever invaded by extrapulmonary cancers Authors who *made extensive studies of metastases to the lungs* did not mention the occurrence of metastases to the bronchi

For the past few years however such cases have been reported The mucosa of the bronchus was found to be invaded by cancer which extended from the parenchyma of the lung or from an extrapulmonary cancer The metastasis had led to thickening of the bronchial wall with protrusion of a mass into the lumen causing bronchostenosis

The condition manifested itself by hemoptyses and cough In some cases the primary cancer was inapparent (silent) in others the manifestations of the metastatic bronchial tumor overshadowed the primary lesion The erroneous diagnosis of primary bronchiogenic cancer was usually based on x ray and bronchoscopic data

Perusal of the histories of the cases reveals that in some of them the diagnosis had been arrived at hastily Thus in one instance the record reads X ray showed a large rounded shadow in the region of the right middle lobe and bronchoscopy revealed tumor protruding from the middle lobe bronchus Tissue was removed and diagnosed carcinoma In another report it was stated X ray examination showed tumor in the lung bronchoscopy showed partial obstruction of the stem bronchus to the right lower lobe ' In both cases pneumonectomies were performed which revealed metastatic tumors in one case it was from a granulosa tumor of the ovary and in another from a teratoma of the testis

It would appear however that hypernephroma is the tumor par excellence which chooses ' the wall of the bronchus As a rule hypernephroma produces spherical or round (cannon ball ') metastases I have observed a case of a woman who eight years after nephrectomy for hypernephroma showed metastatic invasion of the bronchus to the right lower lobe with endobronchial ulceration and diffuse infiltration of the same lobe The diagnosis of bronchiogenic carcinoma was disproved after the bronchoscopic biopsy showed the tumor to be a replica of the hypernephroma removed eight years previously

The protrusion of tumor into the bronchial lumen is not alone sufficient

[a] Cancer of the thyroid breast and kidney metastasize to the lung more often than other cancers

to make a diagnosis of bronchiogenic carcinoma The bronchus as a whole, its dynamics as well as the state of the mediastinum should be studied with care before radical measures are contemplated The clinical history is of significance as is the histology of the tumor

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Chapter V

CLINICAL MANIFESTATIONS

The clinical diagnosis of primary carcinoma of the lungs made great strides in recent years However, the progress usually concerned advanced cases, while incipient ones (minimal) were often overlooked The opinion was held that a diagnosis of early cases is extremely difficult because the manifestations are not pathognomonic frequently masquerading a multitude of other diseases

Cancer of the lung may be divided clinically into three categories

1 Typical, *where the manifestations are essentially respiratory*
2 Atypical, in which the manifestations are due to extrapulmonary disturbances, chiefly metastases
3 Silent, in which the manifestations are inapparent (silent) until the disease has reached an advanced stage

TYPICAL

Many internal diseases produce a characteristic impression on the patient's appearance The impression, however, makes its appearance when the disease is more or less advanced The classical *habitus phthisicus is not an expression of an impending tuberculosis or of a consumptive* constitution" as originally conjectured, but a sign of an existing active or arrested tuberculosis Likewise the characteristic features of individuals with Graves disease or pernicious anemia appear when the diseases have been established

Patients with cancer of the lung are no exception to the general rule An individual with a fully developed cancer of the lung may show changes in the configuration of his thoracic cage, the affected side being 'atrophic" *Due to obstruction of the bronchial lumen or to an adhesive* pleuritis the lung becomes atelectatic, the intercostal spaces narrowed and the respiration lagging There may be a superficial supraclavicular or infraclavicular adenopathy or clubbing of fingers and toes In apical cancers Horner s *syndrome on the affected side is sometimes the first* outward sign of the disease Signs of recent loss of weight or a cachectic hue are conspicuous in many instances

Incipient, preinvasive or early invasive stages of bronchiogenic cancer *do not as a rule, impress their "stamp"* on the individual This holds true of all cancers

THE HISTORY

The past history of patients with bronchiogenic cancer lacks data pertaining to their present illness. As a rule there is no suggestion that familial or hereditary factors are involved.

SIGNS AND SYMPTOMS

Cancer of the lung starts in the wall of a bronchus which it infiltrates causing a narrowing of the bronchial lumen (bronchostenosis) which ultimately leads to its occlusion. The degree of narrowing and the rate of its progress vary from one case to another and in some cases depend on the phase of the disease and on the type of cancer. In some cancers the narrowing is slight even in the advanced stages but in most cases it almost completely obliterates the lumen. The earliest complaints of the majority of patients is related to involvement of the bronchus.

Cough. Cough is the earliest manifestation in about 90 per cent of cases. It may be productive of a serous, seropurulent or mucopurulent sputum or it may be dry, brassy, spasmodic and hacking, predominantly nocturnal. At times it is merely a sort of grunt which is disregarded even by ordinarily apprehensive individuals. Cough is often regarded lightly by patient and physician because of its frequency in non malignant diseases.

Expectoration. The gross appearance of the sputum is not characteristic. Not infrequently it is streaked with blood. About 20 per cent of patients have hemoptysis amounting usually to a teaspoonful of bright red blood but large hemoptyses are rare. A small hemoptysis in a person of middle age is an ominous sign suggestive of malignant disease of the bronchus rather than of tuberculosis or bronchiectasis. It is often the first symptom to attract attention. The expectorated matter frequently contains fine or coarse particles of tissue which should not be overlooked for they may be of value in diagnosis. This will be discussed later on.

Wheeze. A wheezing sound in one side of the chest is often complained of by the patients. It is due to partial occlusion of the bronchus and disappears when the occlusion becomes complete or when the obstructing matter is removed. It is best heard when the examining ear is close to the patient's open mouth. Wheeze accompanied by cough and dyspnea is often mistaken for asthma.

Pain. Patients with primary pulmonary cancer often complain of pain in the chest. In some patients the affected hemithorax is sensitive to slight pressure. By older clinicians pain in the chest was considered pathognomonic and looked on as an early sign. It has been described as persistent, sharp and stabbing with failure to respond to treatment. Brines and Kenning found that in 14.8 per cent of their patients it was the

chief complaint while Frissell and Knox found it only 21 1 per cent of cases The discrepancy in the figures is possibly due to the fact that different stages of the disease were studied Thoracic pain is quite common in the moderately and far advanced stages of the disease but much less often complained of *in the incipient stages* It may be related to stenosis of the bronchus which induces pneumonitis and eventually pleuritis It may also be caused by metastatic involvement of the pleura the thoracic cage or the mediastinal structures

Dyspnea Usually the position rather than the size of the tumor plays a role in the causation of dyspnea Labored breathing occurs when the cancer grows around the bronchi and blood vessels leading to their obstruction and interfering with respiration and circulation In lymphangitis carcinomatosa dyspnea becomes noticeable quite early but it is the right heart failure rather than the carcinoma that is involved Voluminous pleural effusions particularly when they accumulate with rapidity cause dyspnea *in the presence of small tumors* *Severe dyspnea occurs in massive* atelectasis due to occlusion of a large bronchus Finally dyspnea occurs in the Superior Vena Caval Syndrome

This syndrome occurs in instances of obstruction to the flow of blood through the superior vena cava while the circulation in the inferior vena cava remains unimpaired Usually it is caused by aneurism of the ascending aorta malignant lymphoma of the mediastinum carcinoma with metastasis to the mediastinum or by bronchiogenic carcinoma Zeman reported the case of a man of 68 who was under his observation for nineteen years The cause of the obstructive signs and symptoms in the patient had been explained on the basis of a syphilitic mediastinitis with secondary venous thrombosis

The syndrome is characterized by dyspnea edema cyanosis and dilatation of the superficial veins of the chest and neck (fig 43) A frequent feature of venous obstruction of the upper mediastinum is the occurrence *of a transitory edema* of the head and neck on arising in the morning which disappears slowly on assuming an upright position The syndrome is also notable by elevation of the venous pressure and lowering of the circulation time in the upper extremities

Cyanosis *Cyanosis is a condition occurring in instances* of anoxemia — 1

whole lung resulted in cyanosis

Many patients who on postmortem examination showed *nine* tenths of one lung transformed into a solid neoplastic block, and metastases in the other had not been cyanotic during life As in instances of dyspnea the

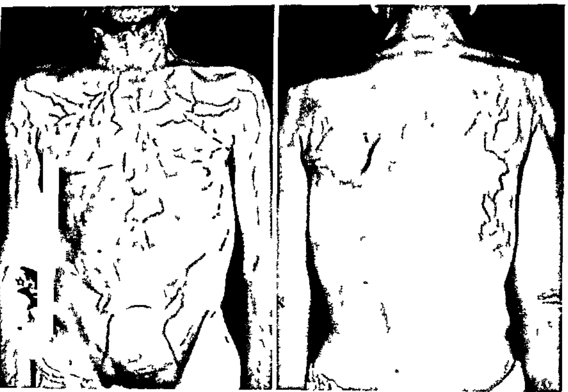


Fig 43 Collateral circulation in a patient with vena caval syndrome Bronchogenic carcinoma of right upper lobe in a man of 60 X ray examination showed a sharply circumscribed mass and an angiogram revealed depression of the right pulmonary artery

occurrence of cyanosis will largely depend upon the topography of the tumor or some complication and not alone on its size Thus in some of our patients a complete block of the bronchus of the right lower lobe and partial block of the bronchi of the middle and upper lobes were present they were dyspneic and orthopneic with a definite asthmatic stridor on expiration yet their cyanosis was not outstanding One patient whose chief complaint was dyspnea and cyanosis of six weeks' duration showed a small pulmonary tumor at necropsy There was, however a hydrothorax and metastases to the pleura pericardium, heart and liver Cyanosis is also a prominent feature in the Superior Vena Cava syndrome

Fever Sporadic episodes of fever whether short or protracted are probably one of the earliest manifestations of carcinoma of the bronchus Elevation of the temperature is not due to a systemic disturbance but is related to involvement of the bronchus, the affection of which finds its prompt repercussion in the pulmonary parenchyma The impairment of the normal dynamics of the bronchus and the destruction of its ciliary columnar epithelium favors the implantation of pathogens in the lung inducing acute or smoldering infections with low grade fever steady or intermittent cough and a state of indisposition As the bronchial lumen narrows the intrapulmonary infection becomes aggravated and the episodes of pyrexia are more severe and protracted (recurrent pneumonia) Many patients state that their disease started with an attack of pneumonia or flu Older clinicians described a type of bronchiogenic cancer with an acute onset They were unaware of the fact that the acute episode was due to the concomitant infection of the lung and not to the cancer per se In 73 per cent of cases bronchiogenic cancer was discovered during or following an acute respiratory infection

Pleurisy Unilateral pleurisy with effusion in a person of middle age may be due to a cardiovascular disease pulmonary tuberculosis or malignancy It sometimes occurs in benign tumors of the ovary—Meigs syndrome Thirty six per cent of patients with bronchiogenic cancer showed the presence of fluid in the pleural cavity at autopsy Many patients admitted to the hospital with no pleurisy developed fluid while under observation The formation of a pleural exudate is usually due to pleural metastases but it may also result from collapse of the lung due to bronchial occlusion It is rarely an early phenomenon When the exudate is hemorrhagic it is almost always due to carcinoma* Cytologic and bacteriologic studies of the effusion provide information as to the nature of the disease

Weight Neither in the early nor moderately advanced stages of bronchio-

* Harrington found a hemorrhagic pleurisy in a patient with a benign neurogenic tumor of the mediastinum

genic cancer is loss of weight an outstanding feature Unlike cancer of the digestive organs patients with carcinoma of the lung maintain their embonpoint for a long time With the advance of the disease a gradual decline in body weight takes place However it is rarely as pronounced as in cancer of the gastro intestinal tract

Cachexia It occurs much less often than in cancer of the stomach or large bowel and is never as severe It is more apt to occur in patients with slowly growing cancers

Night Sweats These are observed in about 12 per cent of patients

Hoarseness The involvement of the recurrent laryngeal nerve either by pressure or by neoplastic invasion leads to hoarseness It is observed in about 8 per cent of advanced cases but rarely in early phases

TABLE 16

Etiology of Fluid in the Pleural Space (Tinney and Olsen

ETIOLOGY	TOTAL CASES	PER CENT OF 274	SEROUS FLUID Number of cases	SEROUS FLUID Per cent of 193	HEMORRHAGIC FLUID Number of cases	HEMORRHAGIC FLUID Per cent of 81
Carcinoma	141	51	82	42	59	73
Congestive heart failure	42	15	31	18	8	10
Lymphoblastoma	28	10	18	9	10	12
Pneumonia	24	9	23	12	1	1
Tuberculosis	16	6	15	8	1	1
Cirrhosis of liver	8	3	6	3	2	2
Chronic nephritis with nephrosis	7	3	7	4		
Miscellaneous conditions	8	3	8	4		

Stridor It is caused by obstruction proximal to the bifurcation of the trachea Older clinicans considered it pathognomonic of cancer of the lung It is rarely observed

Club Fingers Clubbing of the fingers is of frequent occurrence Their appearance sometimes precedes the appearance of characteristic clinical signs I noticed them in 30 per cent of patients The relationship between clubbing of fingers and chronic hypertrophic osteoarthropathy is detailed in Chapter VIII

Horner's Syndrome This syndrome is characterized by sinking of the eyeball, drooping of the upper lid, slight elevation of the lower lid, constriction of the pupil narrowing of the palpebral fissure and changes in the vasomotor and sudorific activities of the skin of ... The syndrome is observed ... as tumors of the spir

eighth cervical or first thoracic segment of the spinal cord cervical rib and carcinoma located in the superior pulmonary sulcu

Adenopathy Metastatic adenopathy in the axillary supra or infraclavicular fossae once considered a rarity is now found in 15 to 20 per cent of cases of bronchial carcinoma Evidently when superficial lymph nodes contain tumor the disease is far beyond the early stages but the finding of such a node in the presence of a suspicious pulmonary lesion clinches the diagnosis



FIG 44 Horner s syndrome on the right in a case of super or pulmonary sulcus tumor

Hemogram The picture of the superficial blood in epithelial malignant disease of the bronchus is not characteristic Some cancers of the viscera produce severe anemia but pulmonary carcinoma rarely causes anemia of significance Hochberg in studying a large number of cases of bronchiogenic cancer found a relatively normal or slightly reduced hemoglobin with a corresponding change in the number of red blood cells per unit volume of peripheral blood a leucocytosis (especially in the afebrile state) with a neutrophilia and rapid sedimentation rate He believes that the described blood picture in the presence of pulmonary disease is strong presumptive evidence of primary cancer of the lung

PHYSICAL SIGNS

In typical cases signs are produced at the onset by irritation (inflammation) of the affected bronchus This holds particularly true of cases in which there is involvement of the main or a lobar bronchus The inflamed mucosa of the bronchus shows hyperemia, hypersecretion, cellular infiltration and desquamation of its normal lining In cases of metaplasia of the bronchial mucosa there occurs occult or visible bleeding similar to that observed in cases of the metaplasia of the lining of the renal pelvis At the onset, with the affection of the bronchus the dynamics of respiration undergo changes there occurs a diminution in the phases of respiration and a diminished expansion of the affected hemithorax

TABLE 17

Early Symptoms in Primary Carcinoma of the Lung

SYMPTOMS	PER CENT
Cough	90
Fever	73
Pain in chest	36
Pleurisy	36
Club fingers	30
Wheeze in chest	5

Of particular significance is the progressive narrowing of the bronchial lumen The bronchus dilates in inspiration and contracts in expiration In the semiobstructive stage, therefore, the ingress of air may be within normal limits (the partial stenosis will be compensated by bronchial dilatation), while the egress will be diminished (the partially stenosed bronchus may be completely occluded in expiration due to expiratory contraction) When the occlusion is partial air is trapped in the alveoli leading to emphysema whereas complete occlusion will lead to atelectasis or collapse of the lung (fig 45) Obstructive emphysema is relatively common in bronchiogenic cancer In some cases it may be so pronounced as to form voluminous (emphysematous) bullae, demonstrated by a roentgenologic examination of the chest in full inspiration and full expiration Signs pathognomonic of emphysema consist in deficient expansion of the chest, tympanitic tone to percussion, and diminished or absent breath sounds The part of the unaffected lung shows hyperresonance and exaggerated breath sounds Atelectasis, lobar or segmental is very frequently found on X ray examination (figs 46 and 47) On physical examination the percussion tone is flat or dull and on auscultation no breath sounds are elicited

There is no bronchiogenic cancer without a concomitant stenosis or occlusion of one and occasionally more bronchi Cases have been observed in which the tumor completely obstructed the upper and middle lobe bronchi, causing atelectasis, and only partly the lumen of the lower lobe bronchus causing emphysema Instances have been reported in which the lumen of the dorsal branch of the bronchus became obliterated while that of the ventral remained either patent or semiobstructed

Pneumonitis What makes the interpretation of the pulmonary signs complex is the advent of a pyogenic infection superimposed on the neoplastic

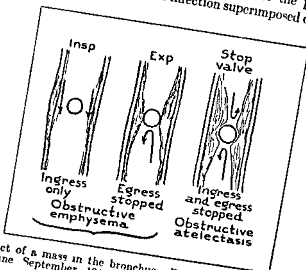


Fig 45 Effect of a mass in the bronchus Diagram adapted by L G Rigler (Modern Medicine September 1944)

infiltration Once the bronchus is affected the lung becomes a ready prey to infection The pathogens inducing bronchopneumonia (pneumonitis) accompanied by fever eclipse the underlying newgrowth There probably has never been a patient with carcinoma of the bronchus who was not treated at the onset for influenza or bronchopneumonia, while the cancer was not suspected

ILLUSTRATIVE CASE

Case 2 *History* A man, aged forty nine, while doing some heavy manual work one day in July, 1933, perceived wheezing sounds in his chest followed by malaise and lassitude Gradually easy fatigability, weakness frequent nocturnal perspirations and occasional afternoon pyrexia were noticed On one occasion he had a severe chill and sharp knife like pain in back occurred He lost his appetite and coughed continually



FIG 46 Atelectasis of right upper lobe due to bronchostenosis A taken in 19?6 interpreted as showing healed fibroid tuberculosis of right apex B one year later

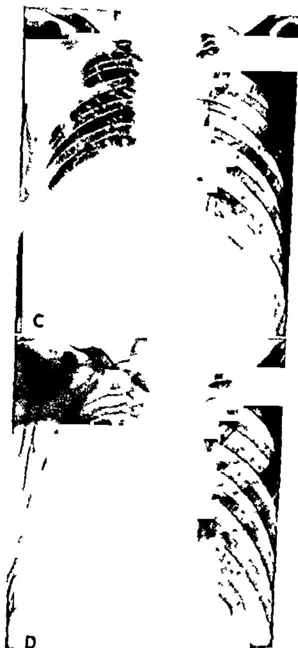


Fig 47 (cont) C and D taken shortly after B

Roentgenologic examination of the chest in October showed that the hilus has completely lost its normal contour on the right side there was a *triangular area of diminished aeration* extending from the hilus to the chest wall. The costophrenic angle on this side was obscured and the homolateral hemithorax was retracted (fig 48). The diagnosis was pneumonitis

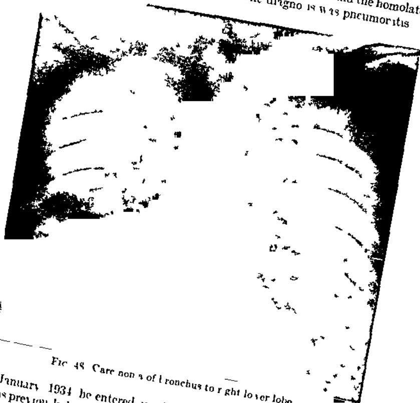


Fig 48 Carcinoma of bronchus to right lower lobe

In January 1934 he entered another hospital where he related that two months previously he had had an episode of pyrexia followed by aggravation of cough and by expectoration of foul smelling sputum. The diagnosis was Pneumonia

Bronchoscopic examination revealed a carcinoma arising in the right main bronchus

Comment The patient's complaints (wheeze in chest and fever) the roentgenologic findings (triangular area of density) and the constitutional symptoms pointed to the diagnosis of bronchial obstruction probably due

to carcinoma Yet the diagnosis of pneumonia was entertained until the bronchoscopic examination revealed the true nature of the disease

In the advanced stages bronchiogenic cancer is apt to be confounded with a number of other diseases (Hodgkin's disease, lymphoma aneurism of the aorta basal bronchiectasis lobar atelectasis, chronic abscess of the lung) but in the early stages the differential diagnosis is limited to but a few

Tuberculosis With few exceptions patients with cancer of the bronchus have at one time or another been considered tuberculous A blood streaked sputum or a minute hemorrhage, characteristic of pulmonary cancer ordinarily served to sustain the erroneous diagnosis The "veiling" caused by apical bronchiogenic cancer has invariably been attributed to tuberculosis in spite of repeatedly negative sputum examinations When cancer developed in a lung with fibrotic tuberculosis the dormant tuberculous infection and not the cancer attracted attention

ILLUSTRATIVE CASES

Case 3 *History* A man of fifty entered the hospital in February, 1930 complaining of intermittent hemoptyses loss of weight and night sweats for eight months His father and brother had died of pulmonary tuberculosis but the patient was in good health until the advent of his hemoptysis After six months of home treatment he was hospitalized Roentgenologic examination showed a rounded area of opacity in the middle of the outer portion of the right lung above which the pulmonary markings were indistinct The diagnosis of pulmonary tuberculosis was made and he was referred to a tuberculosis sanatorium

Hemoptyses persisted and he continued to lose weight at a steady pace but his sputum remained negative for tubercle bacilli Under bed rest he rallied somewhat and was transferred to the Montefiore hospital His cough and hemoptyses continued and the roentgenologic picture remained virtually unchanged (fig 49) The diagnosis oscillated between pulmonary tuberculosis and pulmonary carcinoma

At necropsy an adeno carcinoma of the right upper bronchus was found metastatic to regional abdominal and superficial lymph nodes, also to stomach (leading to ulceration of the gastric mucosa) liver pericardium and both adrenals (fig 76)

Comment Intermittent hemoptyses involvement of the upper lobe and the family history of tuberculosis misled the physician who overlooked the fact that the sputum was persistently negative for tubercle bacilli As else-

Case 4 History A man of fifty-one whose past history was non contributory entered a hospital in April 1937 with the complaint of stubborn cough and steady loss of weight On several occasions he had had hemoptyses and recently he developed pain in chest Examination revealed scattered rales over the chest posteriorly Roentgenologic examination showed incomplete pneumonic consolidation of the right upper lobe with a few

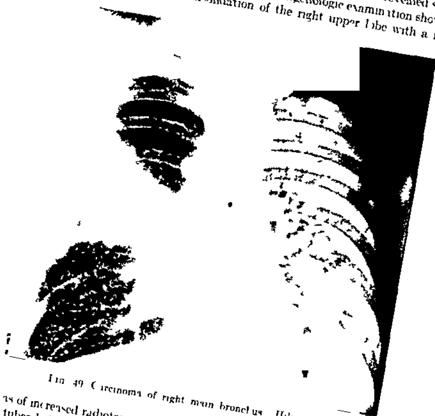


Fig 49 Carcinoma of right main bronchus Hilus type

areas of increased radiotransparency (fig 50) The sputum was negative for tubercle bacilli The diagnosis of tuberculosis was made and pneumothorax induced This was soon discontinued and the patient was discharged

On admission to the Montefiore Hospital he showed evidence of considerable loss of weight with a severe cough and expectoration of blood Roentgenologic examination revealed the presence of pneumothorax and consolidation of the upper lobe interpreted as probably due to tuberculosis

Bronchoscopy revealed a carcinoma of the right upper lobe

At necropsy a squamous cell carcinoma was found in the right main bronchus *metastatic to* regional right axillary and cervical lymph nodes also *to left kidney*

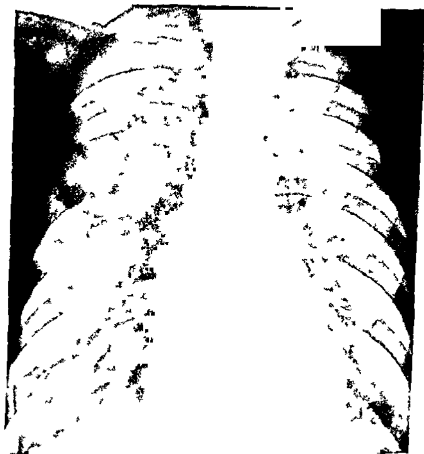


Fig. 30 (Case 1) Carcinoma of the right upper lobe

Comment Analysis of the history of this case in retrospect failed to provide a plausible reason for the diagnosis of tuberculosis and not of carcinoma The unilateral localization of the pneumonic process in the presence of repeatedly negative sputums should have pointed at the outset toward the possibility of a malignant disease The erroneous diagnosis was entertained even in the hospital where the patient was subjected to collapse therapy

Case 5 *History* A woman aged forty three was well until November, 1935 when she developed malaise and cough Her temperature rose to 101 F and nocturnal perspirations appeared She expectorated a muco purulent sputum The diagnosis of broncho pneumonia was made and she stayed in bed three weeks She apparently recovered but by the end of December symptoms reappeared Again she was confined to bed this time



Fig 51 (Case 5) Carcinoma of bronchus to left lower lobe with atelectasis Metastases in right lung

for two months Upon recovery an X ray of the chest revealed a dense area in the left lung diagnosed as tuberculosis Reexamination of the chest three months later seemed to corroborate the diagnosis (fig 51) and she was referred to a tuberculosis sanatorium In this institution too an opaque spot containing a small cavity in the center was visualized in the left lower lobe also minute dense foci in the opposite lung were observed The diagnosis of an atypical form of tuberculous pneumonia of the left lung with spread to the right lung was made Pneumothorax was induced as a diagnostic procedure but was continued as a therapeutic measure

The patient s condition grew worse her cough became more pronounced and her expectoration more copious The pneumothorax was finally discontinued and the diagnosis abandoned

At necropsy an adeno carcinoma of the left main bronchus was found metastatic to contralateral lung, also atelectasis of the left lung with fibrosis

Comment The diagnosis of tuberculosis in this case was based on the patient's elevated temperature on her night sweats and on the presence of a small cavity Roubier believed that there is type *sui generis* of bronchiogenic cancer which induces pyrexia—*cancer fébrile du poumon* We are inclined to attribute fever to infection of the lung a usual concomitant of stenosis of the bronchus In this patient the affected lung was atelectatic and fibrotic As stated earlier individuals with bronchiogenic cancer often suffer from bouts of fever at the very onset of the disease

Tuberculous versus Cancerous Bronchostenosis When tuberculosis is complicated by bronchial stenosis it is particularly apt to be confused with cancer Tuberculosis of the larger bronchi virtually unknown less than a generation ago is now found in about 30 per cent of individuals with pulmonary tuberculosis It usually leads to formation of a scar with retraction and partial (occasionally complete) obstruction of the bronchial lumen inducing pulmonary lesions imitating stenosis produced by cancer of the bronchus

Tuberculous proliferation that takes place in anthracotic tracheo bronchial lymph nodes may lead to deforming bronchitis and gradually to occlusion of the lobar bronchus As in malignant broncho stenosis atelectasis and atelectatic pneumonia develop in the pulmonary lobe and lead to its permanent induration Pneumonectomies have been performed on patients with indurative pneumonia mistaken for cancer The bronchial closure often induces suppurative bronchitis abscesses and gangrene similar to those observed in bronchiogenic cancer Cough productive of blood streaked sputum and occasionally hemoptysis occur in the early stages of the disease

Recurrent episodes of respiratory disturbances accompanied by fever (occasionally by chills) should always be investigated for bronchial obstruction due possibly to bronchiogenic carcinoma

Bronchiogenic Cancer Combined with Tuberculosis of the Lung The association of carcinoma of the bronchus with tuberculosis of the lung is of particular clinical interest In the author's series of cases 11 per cent of patients showed this combination

It was the contention of older clinicians that the tuberculous lesion in these patients was of the healing or healed type and that their sputums were invariably negative for tubercle bacilli Fibrotic fibro cavitary and acute pneumonic types were found in the author's series The sputum was

positive in one third and negative in one half while in the remaining cases it had not been investigated In some patients the originally negative sputum revealed tubercle bacilli after it had been concentrated or cultured on artificial media

As a rule the malignant disease developed in old consumptives Seventy per cent of patients were 50 to 70 years of age In a few instances tuberculosis supervened in an individual who in the past was free from symptoms It is possible that in these cases the walled off tubercle bacilli have been released as a result of immunologic factors It is also possible that the reactivation of a dormant tuberculous infection was due to atelectasis of the lung which is so common in bronchiogenic cancer

The patients may be divided into those whose tuberculosis was asymptomatic at the time when the cancer appeared and those who had symptoms of tuberculosis for years In some of them the malignant disease started abruptly with a severe cold influenza or pneumonia in others it developed insidiously with a steady loss of weight increasing weakness and exacerbation of cough In a few instances the malignant disease was ushered in with a small hemoptysis or with blood streaked sputum It is *significant that cancer was rarely suspected even in patients whose disease* was unilateral and where the sputum was negative for tubercle bacilli Invariably tuberculosis eclipsed the cancer A correct diagnosis was arrived at when a metastasis appeared on the surface

The duration of the illness in the symbiotic group was as a rule no shorter than in patients with carcinoma alone The patients succumbed to cancer and not to tuberculosis

Carcinoma versus Tuberculosis Usually bronchiogenic carcinoma is erroneously diagnosed as tuberculosis but instances have been observed recently in which the reverse took place as demonstrated in the cases to follow

ILLUSTRATIVE CASES

Case C History A machinist 29 years old showed no abnormalities when inducted into the U S Navy in 1943 but on his discharge from service in 1946 an opacity was found at the base of the upper lobe of his right lung The same lesion was found in a dispensary of the Board of Health to which he had been referred for observation Examination of his sputum revealed no tubercle bacilli but it was noticed that the shadow located anteriorly at the level of the 3d rib had grown larger He was asymptomatic and on physical examination no abnormalities were elicited in the chest His past and family history was irrelevant

On admission to the hospital he was found to be well nourished showed no signs of loss of weight and had no complaints Repeated examinations

of the sputum failed to show the presence of *Mycobacterium tuberculosis* Bronchoscopic studies showed no disease of the bronchi, and examination of the sputum and bronchial secretions for the presence of tumor cells was negative

On roentgenologic examination a rounded well circumscribed area of density was found overlying the 2d interspace on the right anteriorly It was located 14 to 16 cm from the posterior wall of the thorax and measured



FIG 52 Roentgenogram on the right shows tuberculosis (rounded shadow in the midzone) mistaken for carcinoma The tomographic appearance of the same shadow is demonstrated in the picture on the left The tuberculoma shows foci of calcification

about 3 cm in diameter (fig 52) Sectional (tomographic) films (fig 52) revealed a round shadow situated in the anterior segment of the right upper lobe with areas of aeration within the shadow on the 9th to 10th cm levels on the antero posterior views and also on the 7th cm level on the lateral view The segmental bronchus leading to the shadow was well outlined on the 8 cm level on the antero posterior views

Two weeks later a hydropneumothorax was seen with the fluid at the level of the 2d rib anteriorly

The diagnosis was bronchiogenic carcinoma and a pneumonectomy was performed

Pathologic Report On examination of the removed lung a tuberculoma measuring 3 5 cm in diameter was found at the base of the upper lobe of the right lung It was partly encapsulated by a thick layer of dense fibrous tissue The caseated material showed numerous tubercle bacilli The rest of the lung contained single and conglomerate tubercles

Comment As stated in the introductory paragraphs the age old error of mistaking carcinoma for tuberculosis is occasionally supplanted by a reverse attitude namely tuberculosis mistaken for carcinoma

To be sure the possibility of the lesion being tuberculous had been considered but was abandoned because of the failure to find tubercle bacilli in the sputum and also because of the atypical aspect of the lesion It may be said that it was no more characteristic of carcinoma Moreover the bronchoscopic examination as well as the sputum and the bronchial secretions were negative for tumor cells Bronchographic studies were regrettably not resorted to and the areas of aeration seen in the center of the shadow in the tomographic films were erroneously interpreted as excavations *occasionally seen in bronchiogenic cancer (cancer of the lung with* cavity or abscess formation) Indeed in the presence of negative physical findings the diagnosis hinged entirely on the laboratory data the roentgen ray films and the sputum examination As already stated the first were not convincing and in the second the important step of animal inoculation was omitted In the case to follow this procedure saved a patient from a pneumonectomy

Case 7 History W B a man 64 years old was admitted to the hospital in May 1947 with the complaints of cough pain in the lower part of his chest on the right side dyspnea on slight exertion and weakness The past and family histories were irrelevant Onset of his illness dated back to the spring of 1946 when he became aware of loss of body weight weakness anorexia and pain in precordium He consulted several physicians and in July 1946 was hospitalized

On examination he appeared somewhat emaciated anemic and dyspneic There was consolidation in the right lower lobe and a small amount of fluid in the right pleural cavity Roentgenologic examination of the chest showed changes interpreted as probable carcinoma of the right lower lobe metastatic to the hilus lymph nodes (fig 53 top) Examination of the *esophagus with barium showed a small irregularity in the anterior wall in* region of the arch of the aorta It seemed to be a walled off opening through the esophagus into the mediastinum A biopsy taken at this spot as well as a bronchial biopsy failed to show tumor The patient was running a tem



Fig 53 (Case ... interpreted as c... in the lower pictur... by an arrow ... of right lo... arance of th... filtration ... as l ... r

perature amounting to 102 F He was treated with penicillin and sulfadiazine resulting in the fall of the temperature to normal but in no improvement of symptoms He remained in the hospital 25 days and discharged

From August 1, 1946 to March 28, 1947 he was treated in the out patient department with X rays He received 2800 r to the right anterior mediastinum and 2200 r to the posterior mediastinum divided into 25 doses

X ray films of the chest taken October 23 1946 showed an increase in the pleural exudate noted on admission In November the fluid occupied one third of the right pleural cavity However, on subsequent examinations in February and April no fluid was discernible

At home he grew worse He lost 24 lbs in weight from September 1946 to April 1947 He suffered from pain in chest weakness shortness of breath Most of the time he was bedridden

On examination at the Montefiore Hospital he was found to be dyspneic and poorly nourished showing recent loss of weight The thorax was asymmetrical, the right side considerably shrunken The respiratory movements on this side were lagging There was an area of dullness to percussion in the right para cardiac region at the base posteriorly The breath sounds were distant and crackling rales were audible Thoracentesis performed in this area yielded 2 cc of fluid which was clear and sterile and contained no tumor cells Examination of the sputum for tubercle bacilli was negative on the usual spread and in cultures

On roentgenologic examination the left lower third of the chest was obscured by a homogeneous density whose outer border extended along the lateral thoracic wall (fig 53 bottom) Above this area there was an irregular triangular opacity apparently a parenchymal infiltration The mesial portion of the lower half of the lung was obscured by another opacity located paracardially The esophagus showed a traction diverticulum 2 cm in length located in the anterior portion of the middle third at the lower level of the aortic arch

A bronchogram revealed some compression atelectasis of the right lower lobe associated with elevation of diaphragm but no bronchial obstruction Tomographic studies yielded no additional data

Bronchoscopic examination revealed no tumor Tissue was removed from the area and on histologic examination showed inflammation with necrosis suggestive of tuberculosis Inoculated into a guinea pig it produced tuberculosis in the animal Likewise the sputum injected into another guinea pig infected the animal with tuberculosis

The patient ran a febrile course his temperature ranging between 101 and 102 F and his general condition remained virtually unchanged A tuberculous infiltration appeared in the infraclavicular region of the opposite lung (fig 53, arrow) He was put on streptomycin 2 gm daily for the first 4

days and 1 5 gm daily for the next 14 days, receiving a total of 29 gm After a few injections his temperature became normal

He was discharged from the hospital with the diagnosis of pulmonary tuberculosis Except for severe dizziness caused by the streptomycin he showed considerable improvement

Comment The diagnosis of carcinoma was based chiefly on the patient's complaints, his steady loss of weight and X-ray films Although the bronchoscopic examination was negative and the bronchogram showed no bronchostenosis the diagnosis of carcinoma was entertained until the microscopic finding of tuberculosis in the bronchoscopically removed tissue The diagnosis of tuberculosis was definitely established when the bronchial tissue and the sputum inoculated into guinea pigs induced the disease in the animals

The roentgenologic appearance of a pleural effusion may occasionally simulate bronchiogenic cancer In the case of a tuberculous pleurisy reported by Aufses an exploratory thoracotomy was performed which served to eliminate the diagnosis of neoplasm but failed to reveal the true nature of the disease Graham and Singer related three cases in which the diagnosis of tumor of the lung was made but on resection the lesions were found to be calcified tuberculous abscesses

Empyema and Carcinoma of the Bronchus Infection of the pleura with the formation of a purulent pleural exudate may be exogenous (introduction of pathogens during thoracentesis) or endogenous (hematogenous, lymphogenous) Tuberculous empyema is formed by direct extension from the affected lung and pleura or by rupture of the lung inducing a bronchopleural fistula and simultaneously a pneumothorax Empyema occurring in bronchiogenic carcinoma is usually caused by rupture of the lung with the outpouring of septic matter from a carcinomatous cavity It is usually accompanied by a spontaneous collapse of the lung In cases of empyema of undetermined etiology the possibili growth obstructing the bronchus should therefore be considere of my patien n empyema thoracis, tuberculosis and c associated in lung The pyopneumothorax suggeste infection and s

proved, but headaches and palpitation developed for which he was hospitalized His lungs showed slight dullness at both bases Roentgen rays revealed irregularly distributed exudative changes in the left upper lobe extending upwards from the enlarged hilus, suggestive of bronchiogenic carcinoma However, as the bronchoscopic examination was negative a diagnosis of tuberculosis was made and he was sent to a sanatorium where he stayed a few months gaining 33 pounds and enjoying good health About one year after the appearance of the first symptoms his cough reappeared, accompanied by elevated temperature and he suffered from pain in the chest He was hospitalized

Examination showed that the expansion of the left hemithorax was considerably diminished and the resonance of the lungs in the left first interspace was impaired The breath sounds were diminished or absent over the entire left upper part of the chest Bronchoscopic examination showed a growth situated between the left upper and lower bronchi compressing both The tumor was a squamous cell carcinoma

A pneumothorax occurred spontaneously on the left side, and in a few days this was complicated by an accumulation of a considerable amount of fluid at first sero fibrinous later purulent Auricular fibrillation set in

Roentgenologic examination of the chest showed (fig 54) an extensive consolidation at the left hilus extending into the parenchyma of the lung Small irregular infiltrations were scattered throughout both left lobes The patient gradually lost ground developed decubitus ulcers and died

At necropsy the upper two-thirds of the left pleural cavity were obliterated There was an encapsulated empyema communicating with a giant cavity which extended to the thoracic wall The left upper lobe in the neighborhood of the hilus was firm and the remainder of the lung necrotic The lumina of the bronchi to the upper and lower lobes were considerably stenosed at the bifurcation and the bronchus to the lower lobe was obliterated by tumor The hilus lymph nodes showed metastases

Comment In this case the empyema was connected with a cavity within the parenchyma of the lung There was a broncho-pleural fistula which permitted air to penetrate into the pleural cavity from the outside inducing collapse of the lung Due to atelectasis the pulmonary markings were obliterated, burying the opaque area which supposedly represented tumor

The occurrence of auricular fibrillation is not very rare in patients with bronchiogenic carcinoma In many cases it can be traced to a coexisting arteriosclerotic or rheumatic disease of the heart in others it is probably related to invasion of the cardiac muscle by metastatic tumor

Bronchiectasis Unilateral basal bronchiectasis complicated by pneumonitis yields physical and roentgenologic signs not unlike those of bronchiogenic



Fig 54 (Case 7) Bronchiogenic cancer and empyema A cancer in left hilus 1931 B two years later



Fig 54 (cont) C spontaneous pneumothorax on the left D pyopneumothorax The last two roentgenograms were taken about six months after that shown in B

carcinoma *Obstruction of the bronchus accompanied by atelectasis episodes of fever blood streaked sputum and constitutional symptoms are suggestive of chronic* bronchiectasis as well as of malignant disease of the lung A painstaking history and a thorough study are essential in order *to arrive at a correct* diagnosis

Bronchiectasis is encountered by far more often in adenoma than in car*cinoma of the bronchus* This is due to the usual tightness of the bronchial occlusion in bronchiogenic adenoma and to the protracted course of the *disease In* bronchiogenic carcinoma a complete clo ure of the bronchial lumen is not always effected, the tumor often crumbles making a fenestra*tion' in the* occluded bronchus and letting air seep in Moreover the duration of the illness in carcinoma is not long enough to allow extensive bronchiectasis to take place

Pneumoconiosis Diseases of the lungs caused by dust may produce symptoms suggesting bronchiogenic cancer Of particular interest is silica which *produces characteristic anatomic lesions Clinically silicosis in*duces cough productive of a muco purulent sputum dyspnea pain in chest *loss of weight and anorexia The physical signs are similar to those ob*served in other fibrotic conditions of the lungs (diminution in intensity of *breath sounds and shortening of the inspiratory phase) While typical sili*cosis is characterized by nodules disseminated throughout both pulmonic *fields and asbestosis by the glass ground appearance of the lungs* there occurs in a number of cases a confluent fibrosis with enlarged hilar shadows *These coalescent fibrotic areas have been mi taken for* bronchiogenic cancer Formerly cancer was invariably mistaken for an inflammatory condition *at present the reverse often takes place*

Bradshaw and Chodoff reported two illustrative cases Their first patient presented symptoms and roentgenologic evidence suggestive of bronchiogenic carcinoma That the patient was exposed to silicious dust for a number of years was known but not seriously considered A thoracotomy was performed the entire lung removed and what grossly seemed to be a carcinoma was found histologically to be a confluent type of anthracosilicosis

Their second patient s complaints were compatible with malignant d s ease of the lung which diagnosis was entertained in three different institutions respectively With the bronchoscope the right bronchus appeared to be almost completely obliterated at the level of the middle lobe attributed to an extrabronchial lesion The trachea was deviated to the affected s de This patient too had been a miner for a number of years and as in the first case no importance was attached to this fact An exploratory thoracotomy was performed and a large firm mass in the upper lobe was diagnosed as carcinoma but under the microscope it was found to be anthraca *silicosis* with extensive fibrosis and consolidation

The problem is still more complex when bronchiogenic cancer is combined with anthraco-silicosis The history of prolonged exposure to dust is of paramount importance Unlike carcinoma the lesion is usually bilateral

Lipid Pneumonia Lipid pneumonia was observed in individuals with a disturbed swallowing reflex who received a vegetable or mineral oil for medicinal or nutritive purposes The oil entered the trachea and the lung where it set up a reaction consisting in the accumulation of macrophages which phagocytosed the mineral and to a slight degree the vegetable oil (fig 55) The extent of the reaction depends on the amount of oil that enters into the respiratory portion of the lung and to the rate of its elimination It may be limited to a few alveoli forming granulomas of microscopic dimensions or it may involve an entire lobe producing fibrosis and obliterating the normal structure of the lung casting a dense shadow upon roentgenologic examination imitating bronchiogenic carcinoma

Since the condition occurs chiefly in debilitated bedridden individuals it is usually superimposed by an infection or it supervenes on top of a smoldering infection which frequently affects invalids The damage to the lung ensuing from the combination of the oil and the pathogens is complex and grave The destruction caused by the bacteria is often underestimated the disaster being attributed solely to the oil However that may be the so-called lipid pneumonia sometimes induces symptoms and signs suggestive of a pulmonary tumor Roentgenologically too the shadow cast by the lesion closely resembles carcinoma Although this type of pneumonia is rarely encountered it should not be overlooked in the differential diagnosis with bronchiogenic carcinoma

In the cases of Janes the diagnosis of bronchiogenic carcinoma was made in individuals who used oil as a nasal drip for a short time one month and two months respectively In the two cases respectively the oil was used 12 years previously In one patient the diagnosis of lipid pneumonia was arrived at after an exploratory thoracotomy and in the other after pneumonectomy

Asthma The early phases of bronchiogenic carcinoma are liable to be overlooked in an individual with asthma because of the cough, dyspnea and the adventitial pulmonary sounds present in these patients The danger of overlooking a malignant disease of the lung is greater in the chronic cougher If an asthmatic of middle age particularly a male, begins to show constitutional changes develops pain in chest or expectorates blood streaked sputum the possibility of cancer of the bronchus should always be considered The occurrence of fever or chills in an asthmatic as in a non asthmatic warrants prompt investigation for bronchial obstruction, possibly of malignant origin Impairment of breath sounds, with or without

changes in the percussion note should be investigated with the same purpose in mind

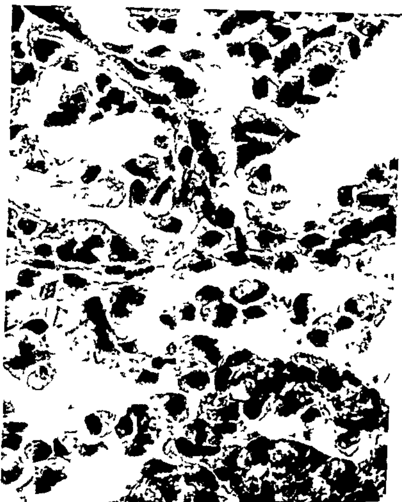


FIG 55 Photomicrograph showing the histology of experimentally produced lipid pneumonia in a cat *The cells lining the walls of the air sacs have increased in size* and number and flooded the air sacs The cells are to all appearances macrophages

Prickham and his associates reported instances in which patients with bronchiogenic cancer were treated as asthmatics while the malignant disease was overlooked

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nodules side by side with conglomerate tubercles. The apex was infiltrated with tumor but showed no tuberculosis. Tubercle bacilli were demonstrated in the left lower lobe. Metastases were found in the regional lymph nodes, pleura, right lung, liver, pancreas, both adrenals, kidney, thyroid, spleen, vertebral column, brain, left temporal bone and pituitary. Microscopically the tumor was a stratified squamous cell carcinoma originating in the left main bronchus.



Fig. 56 (Case 9.) Bronchiogenic cancer of left lung with a huge cavity. A fluid level is indicated by arrow. Tuberculosis is present in both lungs.

Comment. The tuberculosis in this case was of the acute fulminating type and the carcinoma was of the highly malignant variety leading to widespread and unusual metastases. As the destruction of the lung was nearly complete a possible etiologic relationship between the two diseases could not be found. One of the means whereby carcinoma may lead to an exacerbation of an arrested tuberculosis is atelectasis characteristic of bronchiogenic cancer. Atelectasis is instrumental in reactivation of a dormant tuberculosis not only in malignant but also in non malignant conditions.

Supplement II

BRONCHIOGENIC CANCER COMBINED WITH TUBERCULOSIS OF THE LUNG

ILLUSTRATIVE CASES

Case 9 *History* A physician, aged forty, who came to the United States from Germany in 1935, was admitted to the Montefiore Hospital complaining of loss of weight, easy fatigue and cough His symptoms became noticeable about two months previously while he was crossing the Atlantic Prior to his arrival in America he visited Palestine where he contracted Papatocci fever characterized by chills, elevated temperature generalized pains and aches and loss of weight He had three attacks of this infection each lasting about five weeks

On examination he showed considerable loss of weight He had a severe cough productive of a mucopurulent sputum containing tubercle bacilli His temperature was elevated and the erythro sedimentation rate was high The fingers showed slight clubbing

Roentgenologic examination of the chest (fig 56) showed the left dome of the diaphragm and the left costo phrenic sulcus to be obliterated The hilus of the right lung and the trunk markings were thickened, areas of fine mottling were noticed In the left lung there was a uniform diminution of light transmission, and an encysted effusion in the costo phrenic sulcus In the midzone, an area of density with a horizontal upper line was seen also a vaguely outlined area of rarefaction 4 cm in diameter Throughout the rest of the lung with the exception of the extreme apex small areas of mottling were visible Areas of infiltration were scattered throughout the right lung

The impression was that it concerned an advanced stage of pulmonary tuberculosis with a small encysted effusion in the left pleural space and possibly with a small hydropneumothorax on a shelf, or a fluid level in a cavity, in the midzone

The patient developed psychic symptoms suggesting the presence of an intracranial lesion which, however, could not be localized There was a bilateral papilledema but no hemorrhages or exudate

The final diagnosis was Chronic pulmonary tuberculosis, Multiple tuberculomas of the brain

Necropsy Most of the upper portion of the left lower lobe was occupied by a very large thick walled cavity measuring 6 cm by 5 cm , filled with foul smelling matter The remainder of the lobe was firm and contained tumor



FIG 57 (Case 10) Tuberculosis of both upper lobes and carcinoma in right upper lobe A, taken in 1934 B taken in 1938

The acute and relentless course of the disease is noteworthy The occurrence of mental symptoms compatible with an intracranial lesion in the presence of *pulmonary tuberculosis of the lungs*, in this patient, suggested meningo cerebral tuberculosis While the necropsy finding of pulmonary tuberculosis was anticipated, that of a coexisting bronchiogenic carcinoma was a complete surprise

Case 10 *History* A man of 66 was in good health until 1934 when following a "cold" his health began to fail Roentgen ray and sputum examinations were positive for tubercle bacilli The disease was confined to the upper lobes of both lungs *He was referred to a sanatorium* where he improved remarkably and after a stay of seven months was discharged He remained well until 1940, when again he developed weakness and loss of *weight*

Following a fall, in October, 1940, he complained of pain in the left shoulder and within a few days severe knife like pain appeared in the supra scapular region *He was confined to bed for "rheumatism"* but even while bedridden he continued to lose weight and grow weaker He was hospitalized in an institution for consumptives where the diagnosis of pulmonary tuberculosis was reaffirmed However, this diagnosis did not fully explain the patient's symptoms, until a cancerous mass was discovered between the 5th and 6th ribs, probably a metastasis from the lung In the hospital he rallied somewhat and was sent home, but shortly his symptoms became aggravated and he re entered the hospital He was considerably underweight, *dyspneic and his fingers showed clubbing* The upper third of both lungs anteriorly showed impairment of percussion, while posteriorly the upper lobes showed [illegible] fine *rales were heard*

On roentgenologic examination (fig [illegible]) a sharply out[illegible] was visualized on the right side extending from the apex down as far as the fifth rib, posteriorly *The ribs were eroded, the 3rd, 4th and 5th showing* partial absorption A few tuberculous infiltrations were also present in the right upper lobe extending below the tumor mass and throughout the left lung The sputum was negative for tubercle bacilli on direct spread but when concentrated showed the presence of Koch's bacilli

Comment In this case the malignant disease was engrafted on top of a long standing "senile consumption" The two diseases collided but did not seem to affect each other The tuberculosis progressed and the cancer advanced in situ without leading to distant metastases The patient received his *coup de grâce* from the malignant disease rather than from tuberculosis

Case 11 *History* Samuel M a man of 54 whose father had died of carcinoma of the stomach suffered from cough and frequent mild respiratory infections since the age of 15 In the Fall of 1935 his cough became severe and constant and on a few occasions hemoptyses occurred pain in chest developed In January 1936, a roentgenologic study showed the presence of tuberculosis in both lungs As further observation revealed progression

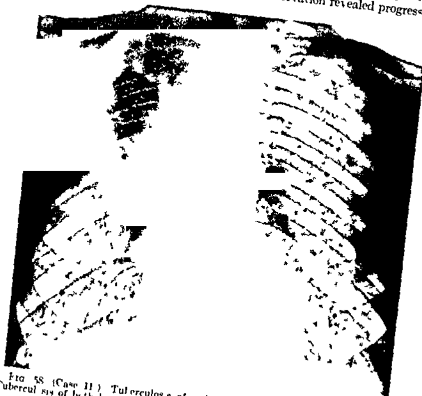


Fig 58 (Case 11) Tuberculosis of right upper lobe with cavity formation Tuberculosis of both lungs

of the disease he was hospitalized A few weeks stay in the hospital brought ephemeral improvement His expectoration became abundant and blood streaked his fingers showed clubbing he lost weight steadily his voice became hoarse

Roentgenologic examination of his chest showed (fig 58) an extensive consolidation of the right upper lobe with a large central excavation and

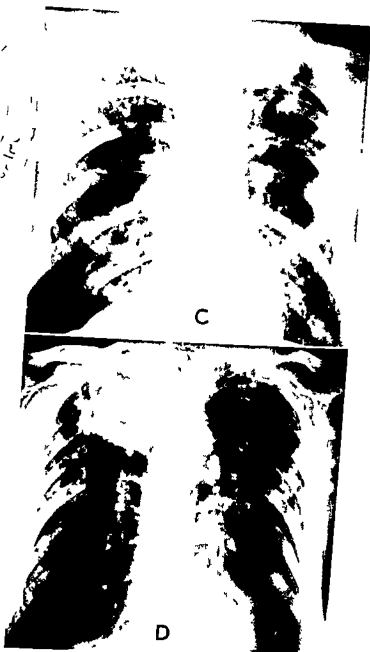


Fig 5" (cont) C taken in 1939 D taken in 1941

rated pure blood. He grew progressively weaker, became dyspneic on minimal exertion and his weight declined. He was examined by several physicians who diagnosed the disease as tuberculosis of the lungs.

On hospitalization he showed evidence of a moderate loss of weight. His thorax was asymmetrical, the left side being atrophic. The respiratory movements on this side were minimal and the sounds heard on percussion

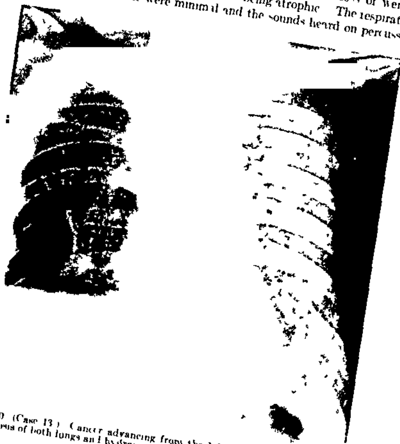


Fig. 60. (Case 13.) Cancer advancing from the hilus to the right upper lobe. Tuberculosis of both lungs and hydropneumothorax on the right.

and auscultation were those of consolidation. There was clubbing of the fingers.

Roentgenologic examination showed (fig. 61) a dense shadow extending from apex to diaphragm on the left side. Several small cavities were seen in the lower lobe. The trachea and heart were displaced to the left side. The sputum was repeatedly negative for tubercle bacilli.

berculosis was arrived at while the cancer was overlooked The presence o cancer in the tuberculous cavity is noteworthy *In this case one was deal ing with a primary double cancer* Cancer of the bronchus and a hyper nephroma

Case 13 *History* A male of 49 dated his illness back four years when following a fall he had a hemoptysis The diagnosis of pulmonary tubercu losis was made but no active therapy was suggested The hemoptysis re curred, the sputum became blood streaked and the cough aggravated He became dyspneic and his cervical veins began to bulge A pleural effusion appeared on the right side

Roentgen ray examination showed a mediastinal mass growing in the di rection of the right upper lobe

Edema of both upper extremities and of chest wall developed and the veins of the neck became markedly distended, those of the abdomen too were large and tortuous

Roentgen ray examination after removal of the pleural exudate showed (fig 60) a dense shadow which almost completely obscured the right lung

The clinical diagnosis was Tumor of the lung with obstruction of the superior vena cava *Bilateral tuberculosis*

At autopsy the right main bronchus showed ulcerated tumor just below the bifurcation expanding *toward the upper lobe which it replaced* *The* tumor encircled the superior vena cava and the end of the azygos vein *The apices contained tuberculosis and bronchiectasis*

The pathologic diagnosis was Squamous cell epithelioma of the right *bronchus* *compression and invasion by tumor of the* wall of the superior vena cava metastases to the regional lymph nodes right pleura diaphragm and right axillary lymph nodes bilateral fibro caseous pulmonary tubercu losis bronchiectasis and right hydrothorax

Comment While clinically the diagnosis was in favor of pulmonary tuber culosis roentgenologically it appeared at the very outset that one was deal ing with a combination of tuberculosis and cancer Hemoptysis is *still* regarded a sign of pulmonary tuberculosis or bronchiectasis However, in individuals past middle age it is pathognomonic of *bronchiogenic carcinoma* rather than of pulmonary tuberculosis

Case 14 *History* Two years prior to his admission to the hospital the *patient* aged *fifty three*, developed a cough productive of mucopurulent sputum On a few occasions it was blood streaked and twice he expecto-

semination of the disease, the small intestines were studded with miliary tubercles and tuberculous ulcers

The pathologic diagnosis was Carcinoma of the left lung chronic fibro caseous tuberculosis of the left lung miliary tuberculosis, bronchiectasis left fibrothorax

Comment It is difficult to explain why the diagnosis of carcinoma combined with tuberculosis was not arrived at in this case Physicians are not yet fully aware of the prevalence of bronchiogenic cancer in the male and the occurrence of carcinoma and tuberculosis in the same lung is considered by them a curiosity

Case 15 *History* A man of 65 who had a mild cough for several years noticed in 1935 that his cough had become aggravated Examination of his sputum revealed the presence of tubercle bacilli and he was sent to a sanatorium where he improved Ultimately, however his cough became aggravated a hemoptysis occurred and his weight began to decline perceptibly Reexamination in another institution confirmed the diagnosis of extensive pulmonary tuberculosis His sputum was negative for tubercle bacilli on the ordinary spread but was positive when concentrated Roentgenologically, the pulmonary changes were interpreted as tuberculous (fig 62) In the left lung the infiltration extended down to the 2nd rib anteriorly, while in the right there was marked involvement of all lobes A dense shadow occupying the mesial two thirds of the right middle and lower lobes was visualized and interpreted as encapsulated fluid Because of the patient's age his loss of weight and the unilaterality of the thoracic signs the diagnosis of carcinoma was entertained A bronchoscopic examination showed an almost complete obstruction of the right lower lobe bronchus Tissue removed by the bronchoscopist was diagnosed as epidermoid carcinoma

The autopsy showed a bronchiogenic carcinoma of the right lower lobe and extensive tuberculosis of the lungs

Comment The carcinoma did not come in contact with the tuberculous tissue The tumor grew slowly and did not metastasize

Case 16 *History* The sole complaint of this patient 56 years old was loss of 24 lbs in three months On examination his lungs showed changes which were ambiguous He suffered from a marked secondary anemia The loss of weight and the anemia suggested carcinoma Roentgen ray examination showed caseous pneumonic infiltration of both lungs, cavities and pleural thickening (fig 63) The sputum was positive for tubercle bacilli The patient declined rapidly and died after a few weeks in the hospital

The clinical diagnosis oscillated between carcinoma and tuberculosis
At necropsy the left pleural cavity was obliterated and the left lung was firm Most of the upper lobe was replaced by a cavity 8 cm in diameter the wall of which was composed of carcinomatous tissue The cavity communicated with the left main bronchus which was infiltrated with cancer



Fig 61 (Case 14) Carcinoma of the left lung with cavity in the upper lobe Tuberculous pneumonia in the same lung and tubercles in the right lung

cells At the point where the bronchus entered the excavation its wall was thick and rigid and its lumen nearly occluded by tumor Scattered throughout the lungs were numerous smooth walled trabeculated cavities There was widespread bronchiectasis Both lungs contained tuberculous pneumonia and conglomerate tubercles There was a hematogenous dis

semination of the disease the small intestines were studded with miliary tubercles and tuberculous ulcers

The pathologic diagnosis was Carcinoma of the left lung, chronic fibrocaseous tuberculosis of the left lung, miliary tuberculosis, bronchiectasis left fibrothorax

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At autopsy the right lung was firmly adherent to the chest wall and showed consolidation of all lobes The greater part of the upper lobe was occupied by a cavity surrounded by a fibrous wall, it also showed acino-nodular tuberculosis and foci of caseation A tumor 4 cm in diameter encircled and virtually replaced a secondary bronchus to the lower lobe The left lung was adherent to the chest wall at the apex The entire upper lobe

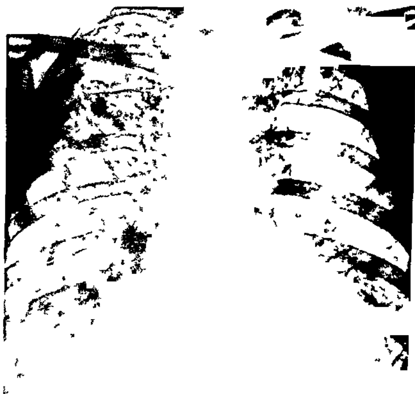


Fig 62 (Case 15) Carcinoma of the left lower lobe and extensive tuberculosis of both lungs

was shrunken containing several communicating cavities Foci of casea ... Fu form ... ronchi were ... g contained large emphysematous blebs

The pathologic diagnosis was Carcinoma of right bronchus chronic bilateral fibro-caseous tuberculosis bronchiectasis and emphysema

Comment Here the malignant disease developed in a lung mutilated by a long standing tuberculous process This case illustrates an ideal symbiosis since the two diseases lived side by side without disturbing one another



Fig 63 (Case 16) Carcinoma of right lung with cavity formation Tuberculosis of both lungs

Case 17 *History* The patient an inveterate smoker aged sixty-one entered the hospital complaining of pain in the back of the neck cough and loss of motion The onset of his cough which was productive of a mucopurulent sputum dated back thirty years Two years before admission to the hospital he developed pain in the neck and noticed that his sputum was

Pott's disease of lower cervical and upper thoracic vertebrae, compression myelitis

Necropsy revealed carcinoma and tuberculosis confined to the left apex. The right lung showed old and recent tuberculosis but no tumor. The hilus lymph nodes, the vertebrae and the liver showed metastases. The cord was compressed by an extradural tumor mass.

Microscopic examination showed the tumor to be a squamous cell carcinoma. It grew in the vicinity of a large area of caseation, and of a dense scar containing carbon pigment and neoplastic cells. In the caseated mass the tumor was seen at the very edge but not in the necrotic tissue. The rest of the lung revealed advanced emphysema and fibrosis with destruction of bronchi and vessels.

Comment. The tumor was situated in the so-called superior pulmonary sulcus; clinically its manifestation was that of a fugitive form of Pancoast Syndrome. Tumor cells were found in the scar. In the past observers had stated that the neoplasm originated in the scar. That carcinoma will not originate in a tuberculous scar which is devoid of epithelial cells is self evident. The scar is invaded by cancer cells from the mucosa of an adjacent bronchus. This case illustrates the association of a superior pulmonary sulcus tumor with tuberculosis.

Case 19. History. A man of sixty five was admitted to the hospital complaining of cough. As a young man he had been employed in a textile mill for about eight years. Subsequently he was employed for sixteen years in a brass factory, where exposed to fumes, he developed a cough which had persisted to date. His present illness dated back one year when it began with a fever followed by weakness and loss of weight (40 pounds in one year). The diagnosis of tuberculosis was made, and he was referred to a hospital.

Examination showed a marked anemia. Beneath the clavicle at the insertion of the sternocleidomastoid muscle a small firm node was palpable. The lungs showed bronchial and broncho-cavernous breathing at the apices and rales elsewhere. The percussion tone was dull. There was a tuberculous laryngitis and the sputum was positive for tubercle bacilli. The supraclavicular node was excised and showed an infiltration with malignant epithelial cells.

The roentgen ray examination showed (fig. 65) fibrotic bilateral pulmonary tuberculosis. The markings at the hilus were greatly increased, suggestive of a neoplasm.

At necropsy the upper lobe of the left lung was firm, containing a sharply demarcated tumor mass about 10 cm in diameter. The remainder of this as well as of the other lung showed scattered conglomerate tubercles and a

blood streaked and this had continued to date Paresthesias and pain in the left hand were of three weeks duration and urinary disturbances dated back a few days only

Examination showed a left Horner syndrome There was weakness of the left side of the body and sensation was dissociated The trachea was displaced to the right Apices of both lungs were markedly retracted The percussion tone was nearly flat bronchial breathing and rales were present



Fig 64 (Case 17) Carcinoma of the left apex and tuberculosis of both lungs

in the apex of the left lung Tubercle bacilli were *found in the* sputum on one occasion

Roentgen examination showed (fig 64) evidence of an old fibrotic tuber

considered

The diagnosis was Chronic fibro caseous tuberculosis of both apice

remained for four weeks No information as to his status there has been obtained Apparently his health remained precarious for following a stay of several weeks with his family he was again hospitalized

Examination showed him to be quite ill He coughed slightly but his weakness was marked His temperature was elevated and he had night sweats In the chest the findings were those of a bilateral tuberculosis



Fig 66 (Case 19) Carcinoma of right lung and tuberculosis of both lungs

with particular involvement of the right upper lobe which was dull to percussion The sputum was negative for tubercle bacilli

The roentgen rays showed an extensive tuberculosis of both lungs The lesion fibrotic in type was fairly evenly distributed showing areas of calcification and a cavity measuring about 3 cm in diameter in the right upper lobe (fig 66)

A firm nodule was found in the right supraclavicular fossa which on his

great deal of fibrosis In the middle lobe of the right lung two small tuberculous cavities were present

Comment The diagnosis of tuberculosis was obvious from the physical signs and from the presence of tubercle bacilli in the sputum However, the excessive loss of weight and the marked anemia remained unexplained until



FIG 65 (Case 18) Carcinoma of left main bronchus and tuberculosis of both lungs

it was ascertained that the superficial nodule was cancerous metastatic from the lung

Case 19 *History* A man of 70 was admitted to the hospital complaining of dyspnea cough and weakness One year before he had contracted a severe "cold" complicated by a cough, productive of blood streaked sputum After an illness of three weeks at home, he was sent to a hospital, where he

scribed, homogeneous mass about the size of an orange There was also an infiltration in the left lower lobe just above the diaphragm The fifth and sixth ribs were destroyed over a distance of about 5 cm The right lung was normal The diagnosis was neoplasm of the left lung or a tumor of the mediastinum The patient died after eighteen days in the hospital

At necropsy the left lung was large and firm The posterior portion of the upper lobe contained a firm white mass measuring about 10 cm in



FIG 67 (Case 20) Well circumscribed pseudo mediastinal cancer of left main bronchus and tuberculosis of right upper lobe

diameter It extended into the parenchyma for some distance and was continuous with the neoplastic tissue which had destroyed a large portion of several ribs and had eroded some vertebrae The adjacent pulmonary tissue was fibrotic containing several small cavities Apices of both lungs contained healed tuberculous lesions and fresh tubercles The apex of the right lung also showed a honeycombed cavity *The diagnosis was fibroid* tuberculosis of apices of both lungs also carcinoma of left lung with invasion of ribs vertebrae and left suprarenal

tological examination showed the presence of carcinoma The patient died after six weeks in the hospital

Necropsy showed a bilateral pulmonary tuberculosis with cavitation at the right apex There also was found a carcinoma of the right lung with metastases to the contralateral lung lymph nodes pleura small intestine pancreas left adrenal and kidneys

The tumor was made up of small round and oval cell with a very scant stroma having the appearance of a sarcoma Tumor was present in the blood and particularly in the lymphatic vessels forming virtually a lymphangitis carcinomatosa At the edge the tumor propagated along the pulmonary septa leading to marked thickening In the close vicinity of the tuberculous cavity tumor cells were seen crowding the adjacent lymphatics and invading the fibrous tissue but not penetrating into the caseous material

Comment As the patient had a firm nodule in the right supraclavicular region which was malignant and as his lungs were full of pathology the diagnosis of a pulmonary tumor was readily made The neoplasm was found in the right lung where the bulk of the bacillary disease was present The left lung showed little tuberculosis It seemed beyond a doubt that the infection with Koch s bacillus had long preceded the neoplastic disease which showed extensive metastases

Case 20 *History* A man aged 71 was admitted to the hospital with pain in the chest His past history except for a non productive cough of many years duration was negative His illness dated back four months when it began with a severe pain in the chest which subsided under the influence of narcotics Following this episode the patient showed signs of failing strength and loss of weight His cough became intense and he expectorated a purulent sputum He was admitted to a hospital where a bronchoscopic examination showed the left wall of the trachea and the left main bronchus pushed to the right and downward as a result of extrabronchial pressure from the left upper lobe

Examination showed a poorly nourished patient with slight clubbing of the fingers The left hemithorax was contracted and its expansion limited Medial to the left scapula was a slightly elevated firm mass The area over the left scapula and downward for about 6 cm was very tender to palpation The percussion tone over this region was flat and one could hear scattered loud rales The resonance was markedly diminished and the breath sounds were barely audible

The roentgen rays revealed the following (fig 67) In the region of the left upper lobe extending from the hilus was a dense sharply circum

Chapter VI

CLINICAL MANIFESTATIONS

ATYPICAL

The first complaints of patients in this category refer to organs other than those of respiration. It is to be expected that cancer of the lung which is apt to disseminate widely will often yield pleomorphic clinical pictures and display a multiplicity of atypical forms. Chronic diseases frequently exhibit protean clinical manifestations. It was common practice among older physicians to look for syphilis in patients with obscure and "irregular" symptoms. The modern physician should be trained to look for cancer in all persons past middle age with vague or complex symptoms.

Of particular importance are patients whose complaints refer to a metastasis, while the tumor in the bronchus remains asymptomatic or presents mild symptoms that are overshadowed by the distant deposit. The atypical category is made up chiefly of this group of patients.

It is well to point out that in some organs (adrenal, liver) metastatic deposits may lie dormant indefinitely, in others they induce early symptoms and in still others they manifest themselves long before the primary tumor. Cerebral and skeletal metastases frequently overshadow the pulmonary manifestations.

METASTASES TO THE BRAIN

Clinical Manifestations. The clinical manifestations of cerebral metastases assume various aspects depending on the site of their location, the number of metastatic foci and rate of their growth. The motor area is apparently the site of choice; next in frequency is the occipital region. However, the leptomeninges, the cerebellum and the cord are not spared. The patients may be divided into two groups:

1. Those whose cerebral symptoms appear while they are under observation for a bronchiogenic cancer.

2. Those whose symptoms of an intracranial lesion are the sole manifestation.

The diagnosis is relatively simple in Group 1 provided one is familiar with this aspect of primary carcinoma of the lung. When a patient with bronchiogenic cancer begins to show personality changes, depression, disorientation or mental and psychopathic abnormalities an intracranial metastasis should be considered.

The tumor was made up of irregularly round cells varying in size from a monocyte to a small lymphocyte Mitoses were not infrequent The new growth was largely necrotic The sections showed healed tuberculous lesions in the vicinity of the tumor

Comment The symptomatology pointed to the diagnosis of a bronchiogenic carcinoma confirmed by the bronchoscopic examination Tuberculosis was unexpectedly found at necropsy Because of the necrotic state of the tumor and the damage of tissues beyond the new growth a possible etiologic relationship between the two diseases could not be ascertained

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Radiation therapy to the skull in order to alleviate symptoms has not as yet been given a sufficient trial

ILLUSTRATIVE CASES

Case 21 History A man of forty nine was admitted to the hospital with the diagnosis of tumor of the brain His illness began suddenly three months before admission with a persistent severe headache followed within a few hours by an attack of general convulsions and loss of consciousness Within the next three days he had had three similar attacks followed by dizziness A month before admission he developed tinnitus in the right ear dysarthria dimness of vision and projectile vomiting

Examination showed swelling of both optic discs and a slight weakness of the left side of the face The localizing signs of cerebral tumor were absent so in order to save vision a right subtemporal decompression was made The patient was relieved by this procedure but soon severe headaches recurred Another occipital exploration was performed and encapsulated, hard tumors were removed The immediate examination of this tissue showed it to be a metastatic carcinoma whose primary origin was not known

Roentgen examination of his chest showed a small area of consolidation in the upper portion of the right middle lobe which resembled an incompletely resolved pneumonia

There was immediate improvement following the operation but a return of the previous symptoms caused a gradual decline and death occurred about nine months from the onset of the intracranial symptoms

The necropsy revealed an adeno-carcinoma of the right bronchus with metastases to the brain (fig 68) adrenal kidneys and lymph nodes

Case 22 History A married woman aged fifty eight was referred to the hospital with the diagnosis of tumor of the brain Her illness had begun suddenly three months previously while she was working at home Her right arm and leg became weak and her vision blurred Her husband noticed his wife's inability to speak intelligibly although her understanding remained unimpaired

On admission she was well nourished A motor aphasia anosmia and a right hemiparesis and hemihypesthesia were present There was a high degree of swelling of the optic discs measured at five diopters Because of this a left osteoplastic exploration was made shortly after admission with the expectation of finding a glioma A tumor was not located but edema of the brain forced the sacrifice of the bone flap There was only temporary improvement death occurred about three and one half months from the onset of symptoms

Patients of Group 2 represent a more complex problem It is desirable to point out that the appearance of signs of an intracranial lesion in a person of middle or past middle age should always suggest the possibility of the lesion being a metastasis from the lung In both groups, respectively the disease may be initiated with amazing suddenness and progress with great rapidity

In patients with a sudden onset, the first manifestations usually consist in general and Jacksonian seizures hemiplegia, and weakness due to involvement of the motor area The disease may start with symptoms of intracranial pressure such as headaches, nausea and vomiting followed by sensory and visual disturbances[6] Bilateral papilledema was observed in some of the patients In a fairly large percentage of cases there occurred involvement of the cranial nerves the facial (peripheral portion) seemed to be affected with greater frequency than other nerves (the fifth or the sixth)

Chemical and cytologic studies of the cerebro spinal fluid will as a rule yield no clue as to the nature of the disease There is at times an increase in the globulin and sugar but no tumor cells have been found

Differential Diagnosis The differential diagnosis between a primary and a metastatic cerebral tumor is frequently baffling The most common cerebral tumor found in persons of middle or past middle age is a rapidly growing *glioma multiforme* showing in a majority of patients early and severe choking of the optic discs However the average period of survival from the onset of symptoms is probably longer in the glioblastoma than in metastatic epithelial tumors varying from several months to a little more than a year depending on whether or not an operative procedure has been carried out

Similarly the differential diagnosis between an intracranial metastasis and a cerebral vascular lesion presents difficulties Here the progressive character of the disease with signs of steadily increasing intracranial pressure would make the diagnosis of a tumor more plausible The same holds true of encephalitis although some degree of papilledema occurs in patients with this disease also

Metastatic cerebral lesions may simulate cerebral thrombosis cerebral hemorrhage brain abscess subdural hematoma and cerebral aneurism

Treatment Treatment of the metastatic lesion is obviously palliative When the patient's condition is good and when the intracranial lesion is localized and presumably solitary surgical intervention with the removal of the tumor is sometimes advisable However, the consensus is that individuals with intracranial metastases stand neuro-surgical procedures poorly their survival following the removal of a nodule being very short

closed The patient had an uneventful recovery but his symptoms increased steadily, his speech worsened, his arms became paralyzed, and a leg became involved When readmitted to the hospital in a semiconscious state he showed a spastic paralysis of the right side with increased reflex, a bilateral ankle clonus and the phenomenon of Babinski on the right, also bilateral choking of the optic discs with hemorrhages, new tissue formation and exudate The diagnosis of tumor in the left temporal region was made and the patient was operated upon A massive partly



Fig 69 (Case 22) A large metastasis in the white substance underneath the cerebral cortex

degenerated tumor was removed which on histological examination was found to be a squamous cell carcinoma

Roentgen ray examination of the chest, after the operation, showed a well circumscribed rounded mass in the left upper lobe anteriorly, extending from the first to the third ribs (fig 70)

Case 24 History A man, aged fifty five was admitted to the hospital for observation The onset of his illness had occurred suddenly with left

Necropsy revealed an adeno carcinoma of the right bronchus with metastases to the peribronchial lymph nodes, the contralateral lung liver, left kidney, left adrenal and brain

Just posterior to the operation site of the parietal lobe there was a single metastatic nodule 3 5 cm in diameter which extended from beneath the cortex toward the adjacent ventricle (fig 69) Search failed to reveal metastases elsewhere



Fig 68 (Case 21) Multiple metastases in the white cerebral substance and in thalamus T tumor

Case 23 History A merchant, aged fifty-six, was admitted to the hospital with paralysis of the right side, headaches, and loss of speech ... when he sud ... ice with slight ... r he had three such attacks associated with paralysis of the right side of the face The diagnosis of a brain tumor was made and a cerebral exploration without a subtemporal decompression was performed No new growth was dis

In case 21 the disease started with generalized seizures followed by tinnitus dysarthria visual disturbances and projectile vomiting In case 22 with hemiparesis and visual disturbances followed by motor aphasia and anosmia In case 23 with twitching of the right side of the face and difficulties in speech followed by facial paralysis In case 24 with facial paralysis followed by disorientation dysarthria mental changes and signs of intracranial pressure



FIG 71 (Case 24) Lining of the meninges by cancer cells from a carcinoma of the bronchus Tumor cells are also present in the subarachnoid space and in the cerebral cortex

In the first three cases the diagnosis was tumor of the brain in the fourth alcoholic psychosis In all the intracranial manifestations appeared suddenly In none were pulmonary symptoms present

METASTASES TO CORD

Case 25 *History* A single woman aged fifty was admitted to the hospital with the complaint of weakness of her left arm Four months prior to admission she had developed a sharp pain in the leg abdomen left elbow joints and left shoulder Two months later she suffered shooting pain migrating from the left shoulder to the right and the occipital region of the head Within a month she noticed a prickling sensation in the left

facial paralysis, disorientation and dysarthria Since the onset mental symptoms and signs of increased intracranial pressure had developed

On examination he was disoriented restless and emaciated There was a left facial paralysis and a slight choking of each optic disc A diagnosis of alcoholic psychosis was made as it was known that the patient was a heavy user of alcoholics Signs of consolidation of the left lung were evident shortly after admission and death occurred sixteen days later



Fig 70 (Case 23) Roentgenogram showing a well circumscribed bronchogenic cancer in left upper lobe

Necropsy revealed an adenocarcinoma of the left bronchus to the lower lobe with metastases to hilus lymph nodes contralateral lung liver adrenals and brain In the brain the metastases were multiple involving the cerebral hemispheres and leptomeninges (fig 71) Metastases were also found in the spinal cord and along the dorsal root ganglion (fig 72)

Comment Cases 21 22 23 and 24 are remarkable in that the first manifestations of the pulmonary cancer were produced by the metastatic intracranial lesion In cases 21 22 and 24 cancer of the lung was discovered at necropsy and in case 23 on roentgenologic examination of the chest after the cerebral exploration

The impression was that the woman suffered from a tumor of the brain or some infection of the central nervous system

Necropsy revealed a left bronchiogenic carcinoma (fig 73) with metastases to regional lymph nodes and spinal cord A well circumscribed tumor 8 by 10 cm was found in the upper portion of the cervical region In some areas the new growth had destroyed the nerve tissue, entirely replacing it, in others it surrounded it in a sleeve like manner No metastases were found in the cerebral hemispheres contralateral lung or other visceral organs

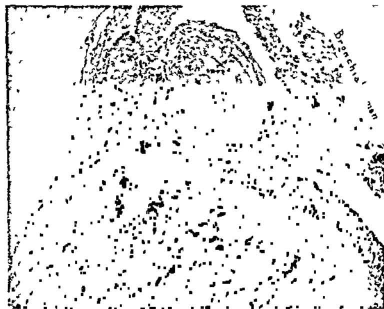


Fig 73 (Case 25) Photomicrograph showing strands of cancer cells embedded in dense fibrous tissue beneath the bronchial mucosa

Comment This case shows the complexity and erratic manifestations of metastatic cancer from the bronchus It is significant that the metastasis grew in one organ only where it attained considerable dimensions It is worth noting that on roentgenologic examination no tumor could be discovered in the lung

METASTASES TO BONES

Clinical Manifestations Pain is an early and nearly constant symptom in the presence of metastases to the bones In vertebral metastases the

hand and simultaneously a marked weakness of the arm At the time of admission abduction of the shoulder and extension of the elbow and wrist was nil For two weeks there has been paralysis of the left leg and disturbance in urination

On examination the left optic disc showed choking of about two diopters There was nystagmus to right and left and upward, loss of conjugate movements of eyeballs above horizontal and a bilateral partial ptosis There was a marked weakness of the left arm the left leg was hypotonic and the reflexes were hyperactive

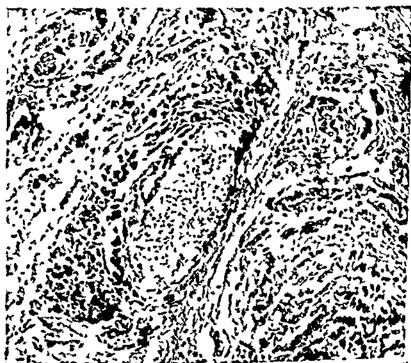


Fig 72 (Case 24) Invasion of the dorsal root ganglion by metastatic cancer cells

A portable X ray film of the chest showed emphysema of lungs but no areas of consolidation

Within a few days following admission the patient became very ill She developed severe headaches, and decubitus ulcers over most of the body prominences A left foot drop and signs of a peripheral neuritis were noted Her temperature rose and remained high

Laboratory examination of body fluids except for glycosuria was negative She died after two weeks in the hospital

of the pelvis an l right femur Th re wa l one production and irregular lepo ts of l one in soft t sue The d agnos s w is osteogenetic sarcoma of the r ght femur met istas z ng to the mediast nal lymph nodes and atelectasis of the r ol t upper lol e The woman d ed after three weeks n the ho p tal



F G 4 Ca e 26) Me as as to bone

Ne rop y eveale l a ri_l t l ron h gen c rc noma itl metasta es to the reg onal lymph n le per ard im l ver adrenals ovary and femur (fig 74)

Comment The pulmonary an l sl eletal symptoms occurred simul taneously but tl e latter v ere dramat c an l oversl a lowe l those of the l ng Pa n n l ones f llo e l l y a pathol g cal fract re p thogn mon c

pain is usually radicular limited to certain dermatomes *and aggravated* by motion cough and straining The distribution of pain in spinal metastases and spinal arthritis respectively is quite distinct In arthritis the painful root zones cover wide areas and include several dermatomes while the radicular pain associated with early metastases to the vertebrae is *confined to narrow zones limited* to one or two roots The serum phosphatase is elevated in skeletal invasion by metastases

Not infrequently symptoms due to *metastasis in the bone appear before* those of the primary pulmonary, sometimes they overshadow them and at times may even be the sole complaint of the patient Occasionally they imitate the symptomatology of multiple myeloma In many instances the disease was ushered in with a spontaneous fracture On roentgenologic *examination they may simulate* a primary osteogenetic tumor *Boyd* reported a case of a boy of 19 who suffered from pains in the bones and diffuse skeletal decalcification As the blood calcium rose to 18 mg per 100 cc of blood a diagnosis of hyperparathyroidism was made However the necropsy revealed a bronchiogenic carcinoma with diffuse carcinomatosis of the bones

It is well to stress that intracranial metastases manifest themselves early while *skeletal metastases remain silent for a considerable time* The roentgen rays may not always disclose their presence Nearly the entire spongiosa of a vertebral body can be replaced by tumor yet not be visualized with the X rays

ILLUSTRATIVE CASES

Case 26 History A woman aged forty two complained of pain in the right hip Her illness *dated back two weeks when swelling* and soreness in the sacro iliac region developed This was followed by pain in the chest and back mild cough and slight loss of weight Roentgenologic examination revealed a tumor in the right femur and hip joints with a pathological fracture of the joint An area of density interpreted as metastasis from the bone was *found in the lung The fracture healed* and the patient was discharged A week later she entered another hospital where analogus findings were recorded An effusion attributed to a metastatic involvement of the lung and pleura was discovered in the right pleural cavity In a third hospital to which *she was admitted two months* later a diffuse thickening of the right pleura *with fluid in the axillary* region was found When the fluid was removed a mass 5 cm in diameter *was disclosed in the right paratracheal* region There was deformity of the right femur and thigh but the hip was not tender and the mobility of the joint was nearly normal

Roentgenologic examination showed irregular rarefaction *in the bones*

bones of the calvarium as well as the pubic were thickened and in places rarefied. The lesion was compatible with Paget's disease. In the skull



Fig 75 Bronchiogenic cancer in apex of left lower lobe

the rarefaction was similar to *osteitis circumscripta*. Roentgenologic studies of the lungs failed to show abnormalities.

The pain grew progressively worse involving the right hip, radiating down the small of the back and through the entire left lower limb to the

of a metastatic tumor Although metastases were present in many organs, only the skeletal produced symptoms

Case 27 *History* A woman of fifty-four complained of pain in the lower back since October, 1934 She was admitted to a hospital where physiotherapy afforded relief for four months after which symptoms recurred with greater severity, particularly in the sacro-iliac region She developed anorexia and loss of weight Roentgenologic studies of the sacro iliac and lumbar regions revealed atrophic changes Examination of the viscera showed no abnormalities

In May, 1935, she developed paraplegia and the following day became incontinent of sphincters, which lasted a few days only She had a flaccid paralysis of both legs, slight ataxia of right finger to nose and tremor of right extended hand She complained of diffuse pain in the abdomen and in the lumbar spine The impression was an extramedullary lesion of the cord due possibly to a metastatic carcinoma

Roentgenologic examination of the chest showed an area of consolidation in the apex of the left lower lobe (fig 75) The outer half of the right clavicle and the body of the 11th dorsal vertebra showed destruction compatible with metastatic carcinoma The patient died after a week in the hospital

Necropsy revealed a mass on the anterior surface of the lower lobe of the left lung Metastases were found in the clavicle and in the dorsal vertebrae causing compression myelopathy The tumor was an adenocarcinoma with mucous formation

Comment Intractable pain in the lower back may be caused by multiple myeloma or by metastatic carcinoma While chemical studies of the blood and urine are helpful in the differential diagnosis, a study of the bone marrow obtained by sternal puncture usually clinches the diagnosis The selection by the metastases of the vertebrae and clavicle is noteworthy Here, too, the alarming skeletal and neurologic symptoms eclipsed the disease of the lung

Case 28 *History* A man, aged fifty four, was in good health until April 1934, when he began to suffer from constant sharp pains in and about the right shoulder, radiating toward the right clavicle In May he was admitted to a hospital where X ray examination of the shoulder showed very marked increase in density of the entire right scapula particularly about the glenoid and coracoid processes' Another X ray picture taken a few days later showed marked condensing osteitis involving the right scapula, near the glenoid the bone appeared to be enlarged There was a fairly large area of rarefaction in the frontal bone, and the

Metastases to adrenals from a bronchogenic carcinoma rarely produce symptoms. However, cases have been described in which the clinical picture simulated Addison's syndrome while the cancer of the lung remained virtually asymptomatic.

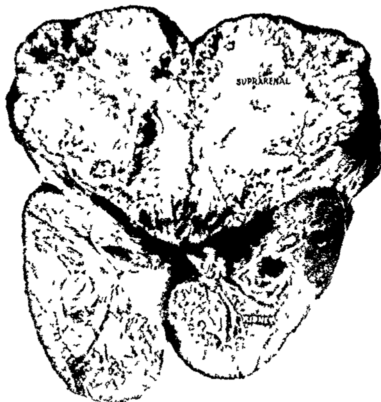


Fig. 76. Cut surface of the right kidney and adrenal. The latter is replaced by cancer leading to a manifold increase in size of the gland. The upper pole of the kidney is compressed (see Case 3

ILLUSTRATIVE CASE

Case 29. *History.* A man fifty-three years old entered the hospital with the complaint of general weakness and loss of weight. For years he had had a non-productive cough which he attributed to the smoking of cigarettes. About two years previous to his hospitalization he noticed that he was losing strength and ambition. Rest at home did not result in improvement. One month before admission his weakness became so marked that he could hardly get out of bed. His appetite had entirely disappeared

ankle For three months before death the patient slept in a sitting position, he suffered severe pain when lying on his back abdomen or side Pain not related to chewing appeared in the maxillary bone, and motion of the shoulder joints became limited The contour of his face showed no change, the head was not enlarged and the legs showed no bowing The cardiovascular and the respiratory systems showed no abnormalities

Reexamined about three months later the bones showed areas of destruction involving the left half of the sacrum, the lower third of the ilium the region of the sacro iliac synchondrosis and the descending ramus of the right pubic bone The right shoulder showed moderate amount of sclerosis of the neck of the scapula and the coracoid process In the body of the scapula just medial to the neck, there was a circumscribed area of bone destruction The bones of the skull were thickened but not destroyed

Roentgenologic examination of the lungs showed a small area of density confined to the apex of the right lung

The skeletal changes were attributed to a metastatic carcinoma but the seat of the primary cancer remained undetermined

Necropsy revealed a carcinoma confined to the upper lobe of the right lung Metastases were disclosed in the hilus and mesenteric lymph nodes liver, left adrenal, ribs and vertebrae The skull, the long bones and the pelvis were not examined

Comment The tumor was a mucous producing adeno carcinoma (see fig 21) Although its metastases were widespread and extensive, only the skeletal yielded symptoms, those of other organs remained asymtomatic

Metastases to bone from bronchiogenic cancer are predominantly osteolytic In rare instances the process is osteolytic in one bone and osteoplastic in another When the metastases are extensive, rapidly progressive and osteolytic, they induce a hypercalcemia Otherwise the laboratory is of no assistance in their detection Pain at the site of invasion and tenderness to pressure are the best signs of their presence

Treatment of skeletal metastases from the breast and the prostate has recently been revolutionized by the use of hormones, androgenic in breast and estrogenic in prostatic cancer The treatment of metastases to the bones from bronchiogenic cancer is chiefly radiation, which leads to alleviation of pain in a large percentage of cases

METASTASES TO ADRENALS

Metastases to adrenals may be solitary and well circumscribed or they may infiltrate the organ diffusely, leading almost to its complete obliteration Sometimes they attain an enormous size as demonstrated in figure 76 The involvement may be uni or bilateral The latter has been reported erroneously as primary bilateral adrenal carcinoma

Metastases to adrenals from a bronchiogenic carcinoma rarely produce symptoms However cases have been described in which the clinical picture simulated Addison's syndrome while the cancer of the lung remained virtually asymptomatic

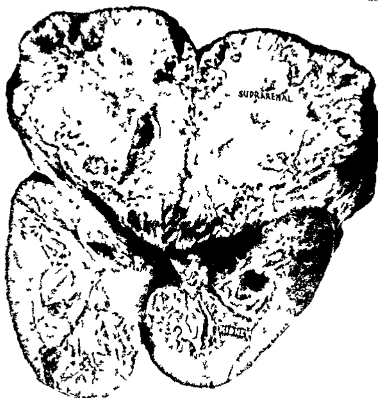


FIG 6 Cut surface of the right kidney and adrenal The latter is replaced by cancer leading to a marked increase in size of the gland The upper pole of the kidney is compressed (see Case 3)

ILLUSTRATIVE CASE

Case 29 *History* A man fifty three years old entered the hospital with the complaint of general weakness and loss of weight For years he had had a non productive cough which he attributed to the smoking of cigarettes About two years previous to his hospitalization he noticed that he was losing strength and ambition Rest at home did not result in improvement One month before admission his weakness became so marked that he could hardly get out of bed His appetite had entirely disappeared

On admission to the hospital he was emaciated The skin was yellowish brown and the mucous membrane in the roof of the mouth showed diffuse yellow pigmentation *The heart and lungs* showed no disease The spleen was about four fingers below the costal margin and had a smooth notch and a sharp edge *A smooth* non tender mass was palpable in the region of the kidney The blood pressure was systolic 96 and diastolic 66

The red blood cells numbered 4,500,000 per cubic millimeter, the white cells numbered 9,600 per cubic millimeter The hemoglobin showed 70 per cent *The differential* count was normal There were no changes in the platelets There was no glycosuria, but the urine contained red cells The phenolsulphonphthalein test showed 40 per cent in two hours and ten minutes 200 cc The basal metabolism was normal



Fig 77 Diffuse infiltration of suprarenal by carcinoma

Stereoscopic examination of the chest showed a marked emphysema with enlargement of the shadow of the left hilus and fibrosis extending from this area toward the left apex

The patient gradually declined On several occasions he had been irrational and at times he was disoriented He died nineteen days after admission

At necropsy a minute tumor was found at the junction of the left primary bronchus and its main branch The tumor extended by projections into the surrounding pulmonary tissue A lymph node at the hilus measuring 5 cm in diameter was studded with tumor Metastases were found in the retroperitoneal lymph nodes, kidneys, brain and both adrenals The right adrenal weighed 50 gms , and the left 60 gms Both had retained their normal color and shape, but were hard as stone (fig 77) A metastatic nodule was found in the frontal lobe of the right cerebral hemisphere

Comment The primary pulmonary tumor was asymptomatic and its

small size was not reflected on the X ray films The clinical course was dominated by the metastases to the adrenals which were virtually obliterated by tumor Hence the picture of Addison's disease At the



FIG 78 Cut surface of the lung showing a carcinoma in the midzone which was clinically silent'

postmortem examination the minute bronchiogenic cancer was overlooked, it was identified after the frozen sections made from the adrenals showed them to be cancerous and not tuberculous, as they had appeared at first

SILENT (INAPPARENT) CANCER

Just as the pathologist speaks of the preinvasive stage of cancer so the clinician speaks of the preclinical phase of the disease How long this

period lasts has never been determined There are however, cancers which attain considerable dimensions without producing symptoms (fig 78) They are discovered by accident during roentgenologic examination or found unexpectedly at necropsy It is the consensus that the bulk of the silent (inapparent) cancers is made up of those which originate at the periphery of the lung in the mucosa of a small bronchiole the ensuing obliteration interferes little with respiration In many cases the "silence" is, indeed, more apparent than real When some of our silent cases were studied in retrospect it was found that the patients displayed bronchopulmonary symptoms which were dismissed as banal The erroneous idea is still entertained that the early manifestations of cancer are invariably dramatic

CONCLUDING NOTE

The diagnosis of bronchiogenic carcinoma in the early stages is a problem which concerns chiefly the internist and the general practitioner rather than the "chest or cancer specialist" who usually sees the disease when it is more or less advanced

The early phases are overlooked for several reasons

1 The disease does not manifest itself until it has reached an advanced stage

2 The manifestations are mild and misleading both to physician and patient

3 Patients fail to seek medical advice until late

4 Physicians fail to diagnose the disease

Bronchiogenic cancer may develop in an individual free from a bronchopulmonary affection or in one who had been a "cougher" for years (bronchitis asthma bronchiectasis tuberculosis chronic pulmonary abscess) The advent of the malignant disease in the first as in the second group is usually not heralded by dramatic symptoms Indeed the mildness of the symptoms at the onset is one of the most frequent stumbling blocks in the detection of cancer in the early stages The diagnosis of cigarette cough or bronchitis is frequently made at this juncture

An intractable cough in an individual of cancer age particularly a male should not be dismissed lightly Aggravation of an existing cough in a "chronic cougher" should be thoroughly investigated

Bronchiogenic cancer is often ushered in with an acute febrile attack ("pneumonia") Repeated episodes of pyrexia (recurrent "pneumonia") occasionally accompanied by chills should be investigated for bronchial occlusion due possibly to cancer

As a chronic disease occurring in persons past middle age carcinoma of the bronchus is liable to be accompanied by degenerative disease and a host of other ailments which often confuse patient and doctor alike

By some authors the disease was referred to as 'masquerading' and 'mimicking' This view reflects lack of familiarity with the protean manifestations of the 'new disease' wh ch h
clinic in our life time The confusing
apparent than real Most of it is large
the seat of a multiplicity of chronic ... ases, particularly tuberculosis Indeed, pulmonary tuberculosis and its sequela or complications still re ma n the chief diagnostic rival of bronchiogenic cancer

In the past other diseases too were considered 'intriguing' and 'mas querading' But a thorough familiarity with their manifestations deprived them of their alleged mysteriousness

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In 1932, I reported a case of a man of forty one whose illness started with sharp pain in the right shoulder, radiating down the arm, right Horner's syndrome, anhydrosis of the right side of the face, right arm and right hemithorax. The necropsy revealed a right apical bronchiogenic carcinoma invading the 6th and 7th cervical ribs, the 1st, 2nd and 3rd thoracic ribs and 1st and 2nd thoracic vertebrae. There were widespread metastases.

SYMPTOMATOLOGY

The symptomcomplex characteristic of apical tumors was based on clinical and roentgenologic observations only. The lack of postmortem verification led to confusion. On one hand, Pancoast claimed that he discovered "a new entity among intrathoractic tumors" on the other hand he stressed "the lack of origin (of these tumors) from the lung and pleura."

Investigation revealed that the symptomcomplex is characteristic of tumors originating in the region of the thoracic inlet and of metastatic tumors that have reached the inlet from other sources. However the latter rarely yield the symptom *in toto*. Only tumors originating *in situ* induce a typical symptomcomplex. It will be shown later that the local tumor probably has two different sources of origin: intrapulmonary (from a small bronchiole) and extrapulmonary (from a branchial rest).

The Brachial Plexus. The first complaint refer to involvement of the brachial plexus. This structure is made up of the anterior primary division of the four (5th, 6th, 7th and 8th) lower cervical nerves and the greater part of the first thoracic nerve. After emerging from their respective intervertebral foramina, the nerves converge toward the upper border of the first rib, unite, form three trunks and then divide into cords from which the nerves of the upper extremity are derived (fig 79).

Pain. Paralysis. The disease begins with pain in one or several points: the shoulder, scapula, upper part of the thorax anteriorly, axilla, ulnar side of the forearm and inside the arm. It is usually restricted to a small area, is not referred to other structures, is quite sharp, burning, shooting or knife like, and shows remissions.

Topographically the pain is related to the involvement of the spinal nerves, or to irritation of the upper thoracic nerves as they emerge from the intervertebral foramina. It may result from encroachment of the tumor on the parietal pleura, which is provided with fibers from the intercostal nerves (fig 80). Stimuli arising in the parietal pleura produce surface pain having a segmental distribution. Ray followed the progression of the pain in successive areas. In one of his cases it began in the scapula and in the upper thoracic region (third thoracic), this was followed by involvement of the inner aspect of the arm (second thoracic), the ulnar side of the forearm and little finger (first thoracic). All nerves of the

brachial plexus may be simultaneously involved When the cervical plexus is affected pain occurs in the side of the neck radiating to the jaw or behind the ear When the trunks are involved the symptoms are radicular but refer to the peripheral nerves when the cords are affected



Fig 9 Diagram of an ana [illegible]

Pain is accompanied by weakness of the arm of the affected hemithorax and this in turn leads to atrophy which begins in the smaller muscles of the hand (the hypotenar and interossei) because of the early involvement of the lower nerves (the eight cervical and first thoracic) forming the brachial plexus

Paresthesias, as evidenced by a sensation of tingling and pins and needles are of frequent occurrence

Two types of paralysis are distinguishable the Duchenne-Erb or upper arm type where there is involvement of the fifth and sixth cervical roots In this type the roots and trunks between the first rib or clavicle and the transverse processes of the vertebrae are compressed The Dejerine Klumpke or lower arm type of paralysis results from the involvement of the nerves derived from the eight cervical and first thoracic root

Horner's Syndrome The syndrome is characterized by sinking of the eyeball drooping of the lower lid slight elevation of the upper lid constriction of the pupil narrowing of the palpebral fissure and change in

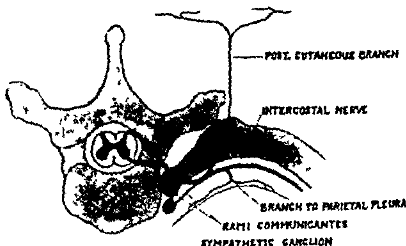


Fig 80 Diagram showing the components of a thoracic spinal nerve (Ray B S Tumors of the apex of the chest Surg Gynec & Obst 67 577 1938)

the vasomotor and sudomotor activity of the skin of the face (figs 14 and 81) It results from destruction of the thoracocervical ganglionic chain at or above the first thoracic sympathetic ganglion In many cases anhydrosis of the face probably precedes the ocular changes This should be expected since the apical bronchiogenic tumors encroach first upon nerves below the first thoracic and thus are apt to yield sympathetic without ocular paralysis at the beginning of the disease

Lindgren reported a case in which the affected side failed to show skin pigmentation equal to the normal side following ultraviolet irradiation The zone of pigmentation was strictly demarcated by the midline and although the face and neck did show pigmentation later on the difference on the chest and back remained marked until the time of death The

failure of the skin to show pigmentation was attributed to involvement of the sympathetic nervous system by the apical tumor

Respiratory Symptoms Cough expectoration and occasionally blood streaked sputum are present in most cases but they are eclipsed by the neurologic symptoms Sometimes they make their appearance while the patient is under observation for the intractable pain in the arm or scapula

Miscellaneous Loss of weight becomes marked in the more advanced stages when pain interferes with sleep and appetite Patients deteriorate chiefly as a result of the narcotics which they consume in large amounts often with slight relief

In a review of 134 cases collected from the literature Herbut found Horner's syndrome in 133 destruction of ribs in 72 and vertebrae in 41 In 129 there was pain in shoulder, in 20 edema of arm and in 99 loss of power in the arm Forty eight patients complained of cough and 6 had hemoptysis There were 137 men and 14 women The right side was involved in 85 instances and the left in 66 All patients succumbed to the disease which lasted on the average 10 5 months Radiation therapy was to no avail

DIAGNOSIS

The symptoms pain in arm and shoulder Horner s syndrome anhydrosis and involvement of the upper three ribs are pathognomonic of advanced cases It is imperative to diagnose the disease in the incipient stages when therapy may be applied effectively

Physical examination will reveal dullness above the clavicle due to infiltration at the apex of the lung and the roentgenologic investigation will disclose a shadow ("veiling") confined to the supraclavicular region The closeness of the tumor to the pleura induces an apical adhesive pleuritis at the onset Later on the supraclavicular fossa becomes fuller and tender to touch (fig 84) Neurologic examination of the area will early reveal affection of the brachial plexus As already said it is possible that the sudomotor mechanism is the first to be affected while the oculomotor comes later

Horner s syndrome is observed in many conditions affecting the cord roots of nerves ganglia and vertebrae Cord lesions at the level of C 7 C-8 and D 1 (cilio spinal center) are associated with this syndrome It also has been observed in patients after a sucessful intrapleural pneumonolysis (attributed to injury of the stellate ganglion Vieussen s nerve or to communicating branches) It may be produced by tumors that have *metastasized to the pulmonary inlet, in close proximity to the plexus* It has been seen in apical neurogenic tumors A positive sputum does not

rule out the simultaneous presence of an apical cancer, for both diseases have been found to be associated in the apex (case 17) Roentgenologic particularly tomographic studies are of assistance in the diagnosis of apical malignancy

ILLUSTRATIVE CASES

Case 30 *History* A man aged sixty eight dated his illness to the Fall of 1937 when he became affected with pain in the right shoulder which radiated to the ulna forearm and hand also with sharp pain in the region of the right scapula The motion and the strength of the hand were not *affected* *A diagnosis of neuritis was made and treatment with diathermy* afforded relief He remained free from symptoms until the summer of 1940 when the illness reappeared Easy fatigability and dyspnea on exertion became apparent but the cough from which he suffered and his weight remained unchanged A lymph node was found in the supra clavicular fossa which on microscopic examination showed *infiltration with* cancer cells

The patient grew progressively worse He became dyspneic weak and suffered from general malaise, he lost weight and suddenly he became aware of awkward movements of his left hand and left leg

Roentgenologic examination of his chest in March 1941 showed pleural thickening over the right upper lobe and some irregularity of the third rib posteriorly A right Horner's syndrome became conspicuous and the right vocal cord became paralyzed Neurologic examination pointed to a metastasis in the right parietal lobe

The necropsy revealed a carcinoma originating in a small *bronchiole* at the apex of the right lung (fig 81) The tumor extended through the thoracic cage upwards involving the subclavian artery and the brachial plexus and metastasized to the contralateral lung and the right adrenal It was a stratified squamous cell epithelioma (fig 82 A)

Case 31 *History* A man aged forty nine who had had a productive cough for three years developed a burning pain in the region of the right scapula and a sharp pain in the anterior part of the right arm radiating down the elbow and high up in the axilla

Roentgenologic examination *of the chest showed a shadow* at the apex of the right lung interpreted as a healed tuberculosis

The pain grew worse resisted medication and interfered with sleep *The* patient was hospitalized for six weeks One month after discharge he was readmitted to the hospital and treated with snake venom and alcohol injections *of the nerve with no improvement* Chordotomy of the second cervical vertebra was then performed and afforded prompt relief and good



FIG 81 (Case 30) Carcin ma at the apex of the right lung The tissue above the tumor is from the neck showing severed blood vessels

neck of the 1st rib while the sympathetic chain embedded in neoplastic tissue projected downward The right pleural cavity was patent The right sympathetic chain was intact, as was the vagus nerve *A thorough examination of both lungs and bronchi revealed no tumor* The tracheobronchial and mediastinal lymph nodes were normal The thyroid larynx pharynx and tonsils were minutely dissected with negative results The heart abdominal viscera genital organs and the central nervous system were negative Microscopically the tumor was a squamous cell carcinoma

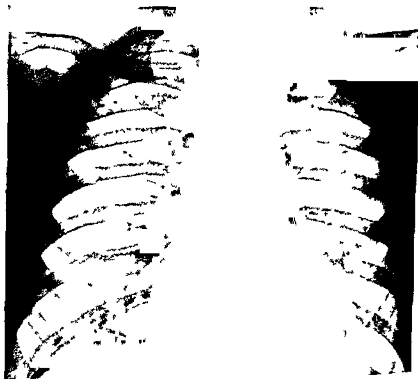


Fig 83 (Case 32) Superior pulmonary sulcus tumor on the left

(fig 85 B) Cancer cells were *found in the ribs* but other structures or organs showed no metastases

Case 33 History A man of forty six entered the hospital complaining of swelling and pain in the left arm painful swelling and pain in the left side of the neck and weakness The onset of his illness dated back nine months when pain appeared in the left arm Within two or three weeks pain developed in the left axilla shoulder elbow hand and fingers Swell

ing of the arm occurred about four weeks before hospitalization and was soon followed by paralysis of the extremity

Roentgenologic studies of the chest shortly after the onset of the illness showed slight intensification of the bronchial tree throughout the lungs with a haziness at the left apex which suggested an old fibrotic type of tuberculosis A firm nodule appeared in the left infraclavicular region it was excised and revealed cancer Within the next seven months the patient received x ray treatment to the upper thoracic region



Fig 84 (Case 33) The appearance of the patient a few months before death There is tumefaction in the region of the left sterno clavicular articulation a homolateral Horner's syndrome and left monoplegia The arm is edematous due to compression of the cervical vessels

Examination at the hospital showed the patient to be considerably undernourished There was a left Horner's syndrome A tender nodular swelling was present in the left supraclavicular fossa (fig 84) The left arm was paralyzed and swollen to twice its normal size The radial pulse on this side was considerably smaller than on the right The percussion note on the left side was dull to the level of the third rib and posteriorly dullness was elicited down to the fifth rib The breath sounds over the left apex were bronchial and distant

The course in the hospital was steadily downward The swelling in the left supraclavicular fossa grew larger and pain in the arm increased Decubitus ulcers developed and death occurred about eleven weeks after admission

At necropsy a mass confined to the left supra and infraclavicular fossae

was found it was firmly attached to the clavicle and underlying ribs and extended down to the third rib The upper lobe of the left lung was considerably compressed from above and was detached from the tumor with difficulty *The pleura clearly separated the lung from the newgrowth which had filled the area above it* Tumor involved the entire length of the clavicle extending to the vertebral column posteriorly, encasing the first second and third thoracic vertebrae The clavicle too was embedded in tumor which had destroyed most of the bone *The second and third ribs showed no tumor beyond the periosteum* Tumor encircled the left axillary artery vein and the brachial plexus The left subclavian and carotid arteries were compressed by neoplastic tissue but in each the lumen was patent The recurrent laryngeal internal jugular and vagus nerves were compressed but not obliterated The thyroid uvula tonsil esophagus pharynx and larynx were normal as were other parts of the body Microscopically the tumor was an exact counterpart of the one found in case 32

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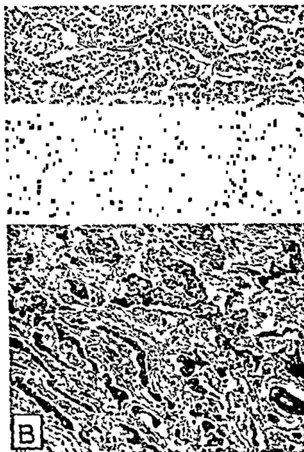


FIG 85 A histology of the intrapulmonary cancer B histology of the extra pulmonary cancer

In the first few weeks of the life of the embryo five bars or branchial arches are present in the region of the neck The depressions between the bars are defined as branchial grooves In instances when a groove persists because of failure to occlude or due to inclusion of epithelial remnants it serves as a point of departure for pathologic processes in that particular region of the neck

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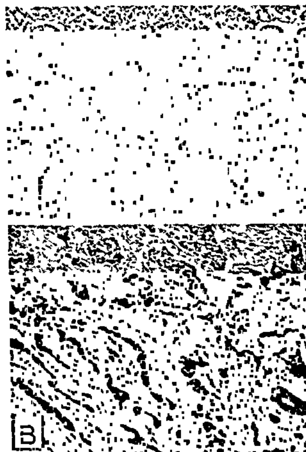


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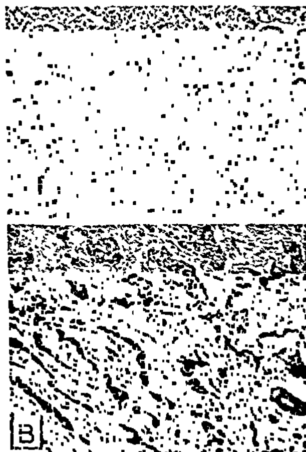


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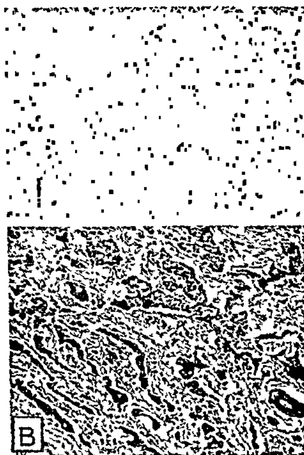


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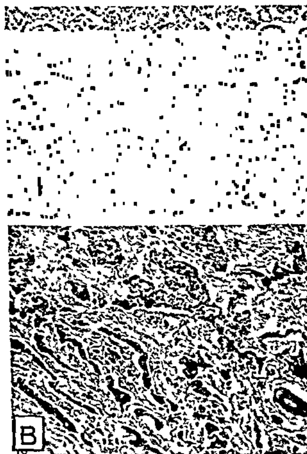


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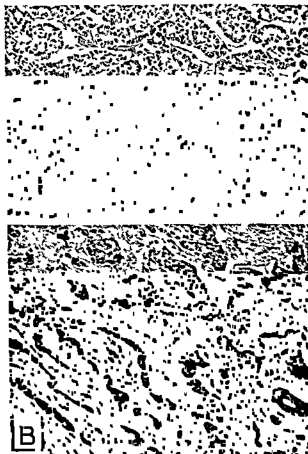


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*Branch*ial (*branch*iogenic) carcinomas are usually situated high in the neck, below the angle of the mandible, in close proximity of the ear and near the sternocleidomastoid muscle They grow around the larger cervical vessels and nerves, leading to circulatory and neurogenic disturbances Microscopically they are squamous epithelial carcinomas

Since fistulae and cysts may develop from any of the clefts including the lower one, it should be conceded, that tumors, too, may originate from

TABLE 18

Summary of Cases

CASE	SEX	AGE	SITE	CLINICAL MANIFESTATIONS	DIAGNOSIS	PATHOLOGY
30	M	68	R	Cough and dyspnea, pain in right shoulder radiating to forearm and hand sharp pain in scapula, Horner's syndrome paralysis of vocal cord	Carcinoma of lung	Squamous cell carcinoma of right apex metastatic to contralateral lung adrenal 3d rib subclavian lymph node brain
31	M	49	R	Cough for three years burning pain in chest posteriorly, sharp pain in right arm radiating to axilla and elbow Horner s syndrome, anhydrosis	Carcinoma of lung	Adeno carcinoma of right apex metastatic to ribs vertebrae temporal bone dura adrenal
32	M	54	L	Sharp pain in left shoulder radiating to elbow atrophy of muscles of left arm Horner s syndrome anhydrosis	Sternoclavicular branchioma	Squamous cell carcinoma invasion of upper four ribs
33	M	46	L	Sharp pain in left shoulder arm and hand paralysis of left arm (monoplegia), Horner s syndrome	Sternoclavicular branchioma	Squamous cell carcinoma invasion of upper three ribs and clavicle

the lower cleft, in the region of the sternoclavicular articulation The appearance of the tumors in cases 33 and 34 and their behavior closely paralleled that of the upper *branch*ial (*branch*iogenic) carcinomas

The foregoing led to the conclusion that the cancers in cases 32 and 33 originated in epithelial rests embedded in the region of the sternoclavicular articulation In accordance with their origin it seemed appropriate to designate them as Sternoclavicular Branchiomas [10]

[10] Herbut suggested that the tumors probably originated in bronchial rather than branchial rests

The symptomatology of the sternoclavicular branchioma like that of its clinical counterpart, the bronchiogenic carcinoma is 'borrowed' from its topography. It is to be noted that the carcinomas were associated with apical tuberculosis and showed widespread metastases, while in the branchiomas no tuberculosis was found in the lungs and the tumors did not metastasize (Table 18). The histologic picture of the branchiomas resembled none of the pulmonary cancers hitherto described (fig 85)

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Chapter VIII

HYPERTROPHIC PULMONARY OSTEOARTHROPATHY

HISTORICAL

Hippocrates is credited with the original observation of pulmonary osteoarthropathy. However, his description referred to the shape of the nails (*ungues adunci fiunt*) which he considered pathognomonic of consumption. The Hippocratic idea prevailed to the end of the past century. Pigeaux wrote in 1832: "The curvature of the nails in the phthisics was not explained by the successors of Hippocrates. The aphorism of this great practitioner had an uneven career. At first it was unanimously accepted. Later its specificity for tuberculosis was denied; it was alleged that it occurs in all diseases accompanied by cachexia. Still later its existence was altogether denied." The noted clinician Trousseau stated: "Not all tuberculous persons have Hippocratic fingers but those who have Hippocratic fingers are, with few exceptions, tuberculous." Esbach, in a monograph published in 1876 noted: "The appearance of the Hippocratic nails (*ongles hippocratiques*) is an important presumption in favor of existing or impending phthisis, provided the heart shows nothing of importance." Esbach found the curved nails (of which he presented numerous illustrations) in circulatory and respiratory disturbances, chiefly in affections with thoracic symptoms. He stressed that the "Hippocratic nail is an extremely serious sign."

The fact that curved nails and fusiform thickening of the terminal phalanges were frequently accompanied by diffuse involvement of the skeleton was overlooked. When similar widespread lesions were observed, they were not associated with clubbed fingers or looked upon as a sequel of a disease of the lungs or heart, but were considered a malady *sui generis*. Indeed, to the latter part of the nineteenth century hypertrophic pulmonary osteoarthropathy was confused with arthritis deformans, acromegaly, Paget's disease of the bones, leonthiasis ossea, and even with osteomalacia, which was not rare in those years. Physicians were ignorant of its pathology and pathogenesis. To Pigeaux (who introduced the term Hippocratic fingers) "the relationship between phthisis and the state of the nails was a complete mystery."

Bamberger, in a brief presentation before the *Wiener medizinischer Gesellschaft* in 1889, was the first to stress that hypertrophic pulmonary osteoarthropathy is found in patients with tuberculosis, bronchiectasis and some

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Chapter VIII

HYPERTROPHIC PULMONARY OSTEOARTHROPATHY

HISTORICAL

Hippocrates is credited with the original observation of pulmonary osteoarthropathy However his description referred to the shape of the nails (*ungues adunci fiunt*) which he considered pathognomonic of consumption The Hippocratic idea prevailed to the end of the past century. Pigeaux wrote in 1832 The curvature of the nails in the phthisics was not explained by the successors of Hippocrates The aphorism of this great practitioner had an uneven career At first it was unanimously accepted Later its specificity for tuberculosis was denied it was alleged that it occurs in all diseases accompanied by cachexia Still later its existence was altogether denied ' The noted clinician Trousseau stated Not all tuberculous persons have Hippocratic fingers but those who have Hippocratic fingers are with few exceptions tuberculous Fsl ach in a monograph published in 1871 noted The appearance of the Hippocratic nails (*ongles hippocratiques*) is an important presumption in favor of existing or impending phthisis provided the heart shows nothing of importance Esbach found the curved nails (of which he presented numerous illustrations) in circulatory and respiratory disturbances chiefly in affections with thoracic symptoms He stressed that the Hippocratic nail is an extremely serious sign

The fact that curved nails and fusiform thickening of the terminal phalanges were frequently accompanied by diffuse involvement of the skeleton was overlooked When similar widespread lesions were observed they were not associated with clubbed fingers or looked upon as a sequel of a disease of the lungs or heart but were considered a malady *sui generis* In deed to the latter part of the nineteenth century hypertrophic pulmonary osteoarthropathy was confused with arthritis deformans acromegaly Paget s disease of the bones leonthiasis o sea and even with o teomalacia which was not rare in tho e years Physicians were ignorant of its pathology and pathogenesis To Pigeaux (who introduced the term Hippocratic fingers) the relationship between phthisis and the state of the nails was a complete mystery

Bamberger in a brief presentation before the *Wiener medizinischer Gesellschaft* in 1889 was the first to stress that hypertrophic pulmonary osteoarthropathy is found in patients with tuberculosis bronchiectasis and some

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Natural History By studying different parts of the bones one finds different stages of the process which has enabled investigators to reconstruct the life history of the disease Thus it was established that the new periost is formed layer by layer the new layer being superimposed on the one already existing which gives to the newly formed structure a lamellary appearance visualized with the roentgen rays Usually the new periost envelops the bone as the bark envelops a tree its surface having a porous or wartlike appearance It is significant that osteoporosis is also present in bones and areas of bones where no new periosteum is formed It is then even possible that the disease originates primarily in the bones and not in the periosteum as is universally believed However that may be the process is that of a hypertrophic porotic osteoporosis As a result the bones are considerably thickened and disfigured they are not elongated

Not only the bones but the soft tissues as well are involved There occur proliferative and indurative changes leading to thickening of the skin and subcutaneous tissue of the hands and feet The skin is soft and doughy but shows no pitting edema

In the joints of the lower extremities there occurs thickening of the periarticular tissues an erosion and in protracted cases disappearance of cartilage Articular effusions have been observed in numerous cases The articular changes may be so severe as to completely disable the patient

PATHOGENESIS

Pigeaux the first to study the phenomenon on a large number of patients noted that it occurs in persons with embarrassed respiration and circulation generally in all conditions affecting hematosis

Marie assumed that bacteria from putrid lungs secrete toxins which affect selectively the bones and the joints

Crump in a study from Erdheim s laboratory stated There is an abnormal substance circulating in the blood which affects the periost the bones the joints and the soft parts of the terminal phalanges as evidenced by clubbing of the fingers

Modern observers adhered to the theory promulgated by Pigeaux in 1832 They repeatedly stated that mechanical obstruction to the flow of blood in the pulmonary circuit and defective oxygenation of the blood are the main factors inducing clubbing of fingers and osteoarthropathy It was assumed that overnutrition of tissues (because of passive hyperemia or vasomotor changes) affecting chiefly the arteries and capillaries result in excessive proliferation of the skeletal system as well as the soft tissues of the extremities

However it was not explained why hypertrophic osteoarthropathy should follow purulent affection of the lungs and not of other organs or

cardiac diseases Almost simultaneously an article appeared by Pierre Marie who accurately described this skeletal deformity and pointed out that it was preceded and accompanied by a long standing disease of the lungs Bamberger, in another and more detailed paper, published in 1891, corroborated Marie's findings

Marie was indeed, the first to separate hypertrophic pulmonary osteo arthropathy from acromegaly The aim of his paper was chiefly to clear away misconceptions I wish at first," he wrote, 'to clear the field of acromegaly of facts not germane to it " He first reviewed a case reported by him previously as acromegaly and found it to be a separate entity By analyzing this case and those with identical symptoms available in the literature, he noted that in all of them the skeletal deformity and the clinical features were not characteristic of acromegaly, also that they were invariably accompanied by a long standing disease of the lungs He introduced the term *Ostéo-arthropathie hypertrophiante pneumique* Since the report of these two physicians the condition was often referred to as Bamberger Marie's or Marie's disease

PATHOLOGIC ANATOMY

The opinion is unanimous that clubbing of the terminal phalanges is a part of hypertrophic osteoarthropathy In instances in which clubbing of the fingers seems to be the sole affection, roentgenologic studies usually reveal characteristic changes in the bones

The bones the periosteum and the soft tissues of the extremities are affected Not all of the bones are involved with equal severity, and even in the same bone the lesion is more pronounced in the diaphysis than in the epiphysis As in all diseases of the skeletal system, the process involves the bone and the periosteum In the former, new bone formation (hyperostosis) is seen here and there The picture, however, is dominated by osteoporosis There is thinning out of the corticalis and the compacta In the periost it manifests itself as a periostitis (osteophytosis)

Structure of the Periost The periost is normally composed of dense fibrous tissue Whenever formation of new bone is called for and whenever there is destruction of bone, a new layer, the *cambium*, is formed on the inner surface of the preexisting periost It differs from the old periosteal layer in its poorer content of reticulum fibers, cellular elements and blood vessels The *cambium*, and not the original periost serves as a matrix for newly formed bone The mechanism of the transformation of the cambium into bone is not understood It may be ushered in by local or general disturbances by action of microbes (syphilis osteomyelitis) or by a general disturbance, as in the cases herein presented It may be localized or it may be diffuse

Case 34 *History* A carpenter, aged forty five, entered the hospital for the first time on October 8, 1932, complaining of pain in the left side of his chest, swelling of the hands and feet and weakness He was married and his wife and child, 5 years old, were in good health, as were his mother and twelve brothers and sisters His father died at the age of 73 of carcinoma of the stomach

The patient became ill in January, 1932, experiencing a general malaise accompanied by fever and cough, productive of a small amount of sputum As treatment at home led to no improvement, he was hospitalized in April, 1932 At this time there were migratory pains in the joints of his hands and feet and pain in the precordium radiating to the shoulder It was noticed that his left eye was ptotic and that his fingers and toes were clubbed The roentgenograms revealed a dense shadow at the apex of the left lung which was interpreted as an old tuberculous lesion The right knee joint showed considerable periarticular thickening and hypertrophy of the synovial membrane with some thickening of the suprapatellar bursa The left showed in addition an inferior suprapatellar bursitis The lower under surface and the shafts of the humeri the radiuses and the ulnas showed productive periostitis The laboratory data were noncontributory He was discharged from the hospital with the diagnosis of fibroid phthisis and chronic pulmonary osteoarthropathy

He grew worse and in July 1932 was hospitalized in another institution where his hands and feet were found to be tremendously swollen A considerable degree of clubbing and cyanosis of the fingers and toes were also recorded There was swelling but not pitting edema of the soft tissues of the hands and feet above the wrists and ankles A roentgenogram of the lungs showed a complete veiling of the left apex the long bones of the hands and feet showed marked periosteal infiltration In this hospital too the diagnosis was tuberculosis of the apex of the left lung and osteoarthropathy

The man's health declined and he lost weight (12 Kg in one year) On one occasion he had a small hemoptysis On October 8 1932 he was admitted to the Montefiore Hospital

Examination The patient was a tall well developed man showing evidence of recent loss of weight, he weighed 58 Kg No dyspnea or orthopnea was noted His skin was dry but normally warm His lower jaw was prognathic (fig 86) and his hands and feet massive the fingers showed clubbing The chest was asymmetric the left hemithorax was flatter than the right The left supraclavicular and infraclavicular fossae were prominent and ten

structures Moreover cases have been observed where this condition developed in the absence of putrid infection While clubbing of the fingers was observed in congenital diseases of the heart and in subacute bacterial endocarditis, *it never occurred in long standing cardiac failure with passive congestion* Likewise it was found in patients with no impairment in circulation

Of particular significance is the fact that hypertrophic osteoarthropathy was observed in individuals with no antecedent pulmonary, cardiac or other visceral diseases It concerned a condition described under various titles cutis verticis gyrata, pachyacria megalia cutis et ossium pseudo acromegaly and acromegalism It was believed that it represented a variety of diseases until Touraine, Solente and Golé produced evidence that in all cases the malady was the same Golé, an assistant of Touraine, abstracted most of the cases in a thesis entitled *Un syndrome ostéo dermopathique pachydermie plicaturée avec pachyperiostose des extrémités* " The disease is characterized by new deposits of periosteum around the long bones, by increase in size of the extremities (squaring), by clubbing of the fingers and toes and by redundancy of the skin of the face and skull Indeed, it is an exact replica of hypertrophic pulmonary osteoarthropathy It occurred in young *males* and, as stated it was not preceded or accompanied by other diseases of the viscera

Hypertrophic Osteoarthropathy and Acromegaly The cases which I have had the opportunity of studying have revealed features which would suggest that the cause of hypertrophic pulmonary osteoarthropathy may not be remote from that of acromegaly and that here too one is probably dealing with an endocrinopathy (dyspituitarism) caused by a disease that originated primarily in the lungs

Patients with this condition have a characteristic appearance their hands are large and spade like and their feet are gigantic Their joints are swollen *and deformed and their feet are doughy and shapeless* They show prognathism and in many not only the extremities but the viscera as well are enlarged (splanchnomegaly) The process in the two diseases affects the same system the mesoderm The pathologic changes may vary in degree and their advance may *differ in tempo but quantitatively* they are essentially of the same nature The anterior lobe of the hypophysis (adenohypophysis) showed hyperplasia of the eosinophilic cells in one of the cases herein presented there was roentgenologic evidence of enlargement of the sella turcica, in another the adenohypophysis was *twice its normal size* As in acromegaly the bones in hypertrophic pulmonary osteoarthropathy are not elongated, their increase in size is due to the increase in the periosteal and the subcutaneous tissues



chus the upper lobe was replaced by a fairly well circumscribed tumor The secondary branches of the upper lobe bronchus were largely obliterated

der on palpation The peripheral blood vessels were not enlarged and there was no superficial edema The left lung showed decreased vocal fremitus over the apex, extending down to the second rib anteriorly and to the third rib posteriorly The percussion note was nearly flat, the voice and breath sounds were diminished, but there were no rales The skin of the forehead showed considerable furrowing The abdominal and pelvic viscera and the genitalia showed no abnormalities There was pain in the left shoulder joint and arm and motion was limited The left eye showed Horner's syndrome (fig 86) The neurologic examination revealed no abnormalities The diagnosis was carcinoma of the upper lobe of the left lung and chronic pulmonary osteoarthropathy

A roentgenogram of the chest taken October 11 showed a dense shadow in the apical region extending from the apex down to and just beyond the first rib anteriorly The shadow was sharply delineated (fig 86) The diagnosis was primary neoplasm of the lung Roentgen examination of the left shoulder showed periosteal thickening along the shaft of the clavicle arthritic changes involving the bone of the shoulder joint and thickening of the periosteum

The patient ran a downward course The Horner syndrome became more accentuated There occurred a destruction of the first, second and third ribs on the left side and erosion of the left border of the corresponding vertebrae Paraplegia developed and he died

Necropsy Gross examination The body measured 168 cm The lower jaw was prognathic The hands and feet were voluminous and showed extreme clubbing of fingers and toes, with very slight edema The edge of the liver extended 4 cm below the right costal margin in the mamillary line The right lung was free of adhesions, but the left was densely adherent to the chest wall above the hilus The apical segment of the left lung was replaced by firm tissue which on separation from the interior portion of the wall of the chest was found to extend up to the base of the neck on the right side, compressing the trachea There was invasion by tumor of the sternal portion of the first rib and of the posterior portions of the first three ribs The left side of each of the first three dorsal vertebrae were also eroded

The heart weighed 470 gm Both ventricles were dilated and hypertrophied but the valves and the coronary arteries were normal The pulmonary ring measured 8 cm , the mitral 10 cm and the tricuspid, 14 cm The thickness of the wall of the left ventricle varied from 8 to 13 mm and the right from 2 to 4 mm The pulmonary vessels were widely patent The aorta showed occasional small atheromatous plaques

The right lung was normal and the pleural cavity patent In the left lung, beginning 2 cm below the level of the bifurcation of the main bron



Fig 86 (Case 31) Bronchiogenic cancer of the left apex Roentgen gran the right hand and left foot showing extensive wartlike periosteal overgrowth tufting of the terminal phalanges In the inset is the patient's acromegalic (ova face showing prognathism and left Horner's syndrome

chus, the upper lobe was replaced by a fairly well circumscribed tumo The secondary branches of the upper lobe bronchus were largely obliterate

by the neoplasm The tracheobronchial lymph nodes contained no tumor. The blood vessels in both lungs were normal No metastases were present in other parts of this lung or in the right lung and no abnormalities were noticed in the bronchi throughout the lungs

The liver weighed 2 000 gm and measured 20 by 9 by 8 cm The right adrenal gland weighed 17 gm and the left weighed 10 gm A minute tumor nodule was visible in each adrenal The right kidney weighed 280 gm and measured 14 by 7 by 5 cm The left kidney weighed 310 gm and measured 14 by 8 by 6 cm Both kidneys appeared large and firm but showed no invasion by tumor tissue The thyroid too was considerably enlarged but there were no visible abnormalities The testes were small and firm

The brain and the meninges revealed no gross pathologic changes The sella turcica was conspicuously enlarged and the pituitary was twice its normal size

Microscopic Examination Histologic sections showed a squamous epithelial carcinoma Tumor cells were present in the perivascular lymphatics and in places in the adventitia of some vessels The adrenals contained a few minute clumps of metastatic tumor cells The striated muscle of the heart showed hypertrophy and fragmentation The liver showed increase in fibrous tissue in the periportal areas but no proliferation of the bile ducts the configuration of the lobule was preserved The spleen showed areas of amyloid There was atrophy of the testes, with no spermatogenesis In the pituitary there were hypertrophy and extensive proliferation of the eosinophilic cells

Comment The principal lesion in this case was a carcinoma of the left pulmonary apex a so called Superior Pulmonary Sulcus Tumor In two hospitals where the patient was observed prior to his entry to the Montefiore Hospital the veiling of the apex was identified as tuberculous and not carcinomatous There was no suppuration of the lung or the tumor at the postmortem investigation

The appearance of the patient was that of a person with acromegaly the face was oval and the chin strong the hands were voluminous and spade like and the feet were gigantic This was due to the characteristic periosteal overgrowth as well as to the increase in size of the soft tissues which were swollen without revealing traces of pitting edema It is not understood why megalia cutis et ossium should make its appearance in one case and be absent in others

Not only the extremities but the viscera as well were enlarged the patient showed a splanchnomegaly As his weight before death was only 52 kg the weight of his heart (470 gm) spleen (430 gm) kidneys (620 gm) and adrenals (27 gm) should be considered as enormously increased

Tufting of the terminal phalanges characteristic of acromegaly was present in this case too

Finally the pituitary gland was twice its normal size, revealing a pronounced hyperplasia of the eosinophilic cells The testes showed atrophy of tubules with no spermatogenesis

Case 35 History A married woman of 61 entered the Montefiore Hospital complaining of weakness and constant pain in the legs Her husband and five children were alive and well One child had died at the age of 5 of croup There had been one miscarriage at the third month of pregnancy following a fall Seventeen years prior to her admission after an episode of irregular vaginal bleeding her uterus and tubes were removed In 1925 she underwent a perineal operation complicated by an abscess of the right lung which subsided spontaneously In 1929 her gall bladder was removed it was inflamed but contained no stones

Her present illness began in the fall of 1940 with a cold which persisted for two months after which a cough productive of small amounts of sputum developed Simultaneously her appetite began to deteriorate and soon pain in the knee joints and legs set in her fingers commenced to show clubbing

In February 1941 she entered a hospital where it was noticed that her features were heavy and her skin was coarse dry and thick Her fingers and toes showed a marked degree of clubbing the nails were beak shaped Nothing abnormal was found in the lungs She was discharged unimproved A few weeks later she entered the Montefiore Hospital

Examination The patient was obese despite evidence of recent loss of weight Her skin was gray and coarse There was no apparent thinning of the eyebrows the upper lip showed a considerable degree of hirsutism Her tongue was noticeably enlarged (macroglossia) and its dorsum was coarsely furrowed (fig 87) There was rounding of the shoulders and the lips were thick There were deep corrugations of the scalp resembling the bulldog scalp as described by American authors in acromegaly It could be picked up in large folds especially around the occipital region (It could not be photographed because of the growth of hair on the head which the woman refused to have removed) Over the forehead face and upper eyelids the skin was thickened furrowed and redundant Forearms hands legs and feet were enormously enlarged The length of the fingers was not affected but they showed pronounced clubbing (fig 87) and their circumferences as well as those of the hands were greatly increased The ankles and feet were swollen with pronounced enlargement of the feet and toes of the same character as in the upper extremities The circumferences of

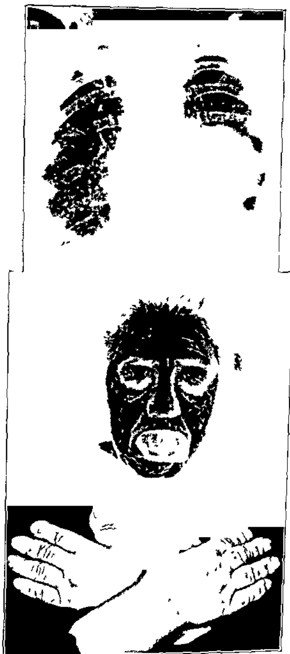


FIG 87 (Case 35) Roentgen appearance of cancer of the lower lobe of the left lung Photograph of the patient, with redundant eyelids macroglossia, swollen hands clubbed fingers and hirsutism

various structures of the upper and of the lower extremities are shown in the table

STRUCTURE	CIRCUMFERENCE		STRUCTURE	CIRCUMFERENCE	
	Right	Left		Right	Left
	cm	cm		cm	cm
Thumb	6	6	First toe	10 75	10 50
Index finger	9 5	9 5	Second toe	6 75	7
Middle finger	9 75	9 5	Third toe	7	6 75
Ring finger	9 25	9 5	Fourth toe	6 75	6 75
Little finger	9	9	Fifth toe	6 5	6 5

The circumference of the right wrist was 20 5 cm and of the left 19 5 cm, of the right palm 22 25 and of the left 21 The right foot at the ankle measured 28 cm in circumference, the left 29 the right calf measured 31 5 cm and the left 31 5 There was extreme tenderness of the bones of the hands and wrists, also of the lower ends of the radiuses and ulnas The outer third of the clavicle, too was extremely tender The neurologic examination showed no abnormalities, and a bronchoscopic study failed to reveal an endobronchial lesion

Laboratory Data The basal metabolic rate was + 1 per cent The hemoglobin content was 71 per cent The white blood corpuscles numbered 7,200 per cubic millimeter, with a normal differential count The urine was normal The concentration of sugar in the blood was 123 mg per hundred cubic centimeters of blood, of urea 11 4 mg of cholesterol 158 mg, of calcium 9 4 mg, of phosphorus 3 3 mg of albumin 3 8 mg and of globulin 2 4 The phosphatase activity was 5 3 Bodansky units The blood pressure was 112 systolic and 78 diastolic

Roentgenologic Examination Chest A large circular sharply delineated mass about 3 cm in diameter was seen extending from the left hilus (fig 87) A lateral view revealed the mass to be situated in the midportion of the lung probably in the upper lobe close to the hilus

Left Shoulder Including the Upper Two Thirds of the Humerus There was an irregular periosteal thickening of the bone along the entire shaft of the humerus and along the outer third of the shaft of the clavicle Hyperostotic changes involved the acromion process of the scapula with periosteal thickening along the lateral border

Right Shoulder There was periosteal thickening of the bone along the outer third of the shaft of the clavicle and periosteal thickening along the medial aspect of the upper third of the shaft of the humerus and the lateral aspect of the lower third

Hands There were extensive deposits under the periosteum of the phalanges and metacarpal bones (fig 88)

Left Forearm There was irregular periosteal thickening along the shafts of both bones The thickening was most pronounced along the upper third of the shaft of the ulna and was similar to the changes noted in the hands and feet

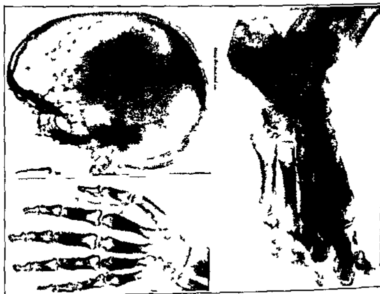


Fig 88 (Case 35) Thickening of the bones of the cranial vault Roentgen appearance of hand and foot, with extensive periostitis and tufting of the terminal phalanges of fingers and toes

Legs Irregular periosteal thickening was observed along the shafts of both bones

Feet There were extensive irregular subperiosteal deposits along the shafts of all the metatarsal bones and the proximal row of phalanges (fig 88) There was also periosteal thickening along the medial and lateral aspects of the shafts of the femurs The terminal phalanges of the fingers and toes showed tufting (fig 88) The sella turcica was not enlarged, but the cranial bones were thickened

The clinical diagnosis was Acropachyderma with pachyperiostosis, tumor of the lung

Tissue obtained by aspiration from the mass in the chest visualized with roentgen rays showed the growth to be a squamous cell carcinoma. The woman died after seven months in the hospital. Autopsy was not performed.

Comment. The appearance of this patient was so striking that the mass visualized in the lungs was relegated to a second rank and the interest was centered on the identification of the extrapulmonary condition. The two diseases were thought to be independent of each other.

Myxedema, to be sure, was the first diagnosis that came to mind. But that she had no hypothyroid disease soon became apparent from her normal basal metabolic rate, her voice, her skin and from other signs.

Her general appearance strongly suggested acromegaly of the massive type (*type massif*) as opposed to the giant type (*type géant*) described by Marie. Similar to patients with acromegaly, she showed involvement of the skeleton with the characteristic changes of the terminal phalanges and soft tissues. Her tongue was enlarged (macroglossia), her features coarse, her eyes puffy, her skull thickened and her scalp redundant ("bulldog scalp").

The characteristics enumerated brought to mind another disease described under various titles: cutis verticis gyrata, pachyacria, megalia cutis et ossium, pseudoacromegaly and acromegalism. Originally it was believed that the condition represented a variety of diseases until French clinicians produced evidence that in all cases the malady was the same. Brugsch, in a report of a case, thought the name "acropachyderma with pachyperiostosis" more suitable. The malady is characterized by new deposits of periosteum around the long bones, by increase in size of the extremities, by clubbing of the fingers and toes and by redundancy of the skin of the face and skull. It is an exact counterpart of the osteoarthropathy found in bronchiogenic cancer.

Case 36. *History.* A childless widow 55 years of age entered the hospital in September, 1932, complaining of productive cough and pains in the upper and lower extremities. Early in 1930 she had been affected by postprandial attacks of vomiting, which were relieved by dieting and gastric lavage. With her respiratory difficulties unabated she was admitted to a hospital where a roentgen examination revealed a shadow occupying the mesial portion of the lower half of the upper lobe of the right lung. With the bronchoscope, an infiltration of the right main bronchus extending into the upper lobe bronchus was seen. She was subjected to treatment with roentgen rays but this was soon abandoned because of repeated hemoptyses and con-

stant blood streaking She was discharged from the institution unimproved

The mild pain in the extremities which had existed for some time became aggravated, and motion became painful She lost weight and strength She was then hospitalized at the Montefiore Hospital

Examination She appeared frail and undernourished Her chin and upper lip were covered with a thick growth of hair The hirsutism had appeared about one year previously, at which time her skin began to take on a brownish hue There was considerable puffiness around her eyes, giving her a mongoloid appearance There was a general adenopathy, and the cervical veins showed dilatation Her extremities were massive, in contrast to her frail body, which weighed 40 kg The extremities throughout their entire length were thick, round and shapeless, which gave her a grotesque appearance The hands were wide and spadelike The distal phalanges were clubbed, and the distal portions of the radiuses and ulnas were greatly widened There was no pitting edema

The right hemithorax was retracted, and the trachea was deviated to this side There was dullness to percussion, and rales were heard throughout the entire right lung, the left lung showed no abnormalities The liver was palpable several centimeters below the costal margin, but there was no tenderness on palpation of the abdomen The blood pressure was 160 systolic and 100 diastolic There was a mild hypochromic anemia The basal metabolic rate oscillated between −18 and −25 per cent There was severe trismus, the separation between the upper and the lower jaw being no more than a few millimeters, only by force could the separation be made

Roentgen Examination Chest A fairly large mass, the size of a lemon, extending from the right hilus and spreading toward the parenchyma was noticed The middle and lower lobes contained a few metastatic nodules, and the pleura seemed to be thickened (fig 89 A)

Bones The bones were moderately atrophic, showing extensive periosteal thickening along the entire length of the shafts of the humeri (fig 89 B) The hands revealed periosteal thickening along the metacarpal bones, the phalanges, the radiuses and ulnas There was tufting of the terminal phalanges, fingers and toes

Course The patient declined slowly and died after several months in the hospital

Necropsy Gross Examination The body was that of a poorly developed and considerably emaciated woman, 145 cm in length The skin was pale and sallow, the hair was gray, coarse and thick The upper eyelids were puffy, producing a mongoloid appearance The chin and upper lip were abundantly covered with hair All extremities showed a high degree of osteoarthropathy The distal phalanges revealed a pronounced clubbing and the distal portions of the arms a noticeable widening



FIG. 89 (Case 39.) A, cancer of the lower lobe of the right lung. The right humerus shows periosteal overgrowth. B, roentgen appearance of the left hand, with periostitis of the phalanges, ulna and radius and atrophy of bones and tufting of terminal phalanges.

The left lung was free from adhesions and appeared normal; the right was firmly adherent to the chest wall. It was about one half the size of the left,

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Course The patient declined slowly and died after several months in the hospital

Necropsy Gross Examination The body was that of a poorly developed and considerably emaciated woman 145 cm in length The skin was pale and sallow the hair was gray, coarse and thick The upper eyelids were puffy producing a mongoloid appearance The chin and upper lip were abundantly covered with hair All extremities showed a high degree of osteoarthropathy The distal phalanges revealed a pronounced clubbing and the distal portions of the arms a noticeable widening

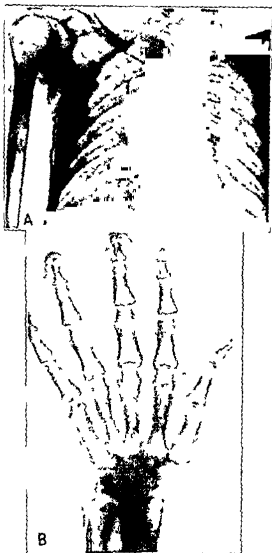


Fig. 89 (Case 36). A, cancer of the lower lobe of the right lung. The right humerus shows periosteal overgrowth. B, roentgen appearance of the left hand with periostitis of the phalanges, ulna and radius and atrophy of bones and tufting of terminal phalanges.

The left lung was free from adhesions and appeared normal, the right was firmly adherent to the chest wall. It was [illegible] half the size of the left,

its pleura measuring 5 mm in thickness The upper lobe was fibrous and atelectatic At the hilus all lobes showed infiltration by a tumor mass measuring 3 5 cm in diameter The growth began about 1 cm below the bifurcation and grew downward along the peribronchial tissue, virtually enveloping the bronchi The right main artery was surrounded by the greatly thickened pleura, which was infiltrated by tumor, narrowing its lumen The superior vena cava, too, was encircled by the thick pleura which distorted its course and narrowed its lumen The tracheobronchial lymph nodes were invaded by tumor The heart, liver, kidneys and spleen were normal in appearance The left adrenal gland showed a cortical adenoma measuring 0 5 cm in diameter The thyroid showed several adenomas The uterus contined myomas, and the ovaries were small and fibrous The brain, the pituitary body and the pineal gland appeared normal

The anatomic diagnosis was bronchiogenic carcinoma of the right lung with metastases to the left lung, the left kidney, the spleen and the vertebral column, hirsutism cortical adenoma of the left adrenal, adenoma of the thyroid, myoma of the uterus diffuse pulmonary osteoarthropathy

Microscopic Examination Histologically the tumor was a squamous epithelial carcinoma The diseased lung showed wide areas of fibrosis due apparently to radiation therapy The thyroid showed a moderate degree of colloid goiter and several adenomas The adrenals, too, showed a sizeable adenoma In the pituitary there was hyperplasia of the cells of the anterior lobe with eosinophilic elements in the majority

Comment In this case the tumor originated in the mucosa of the right main bronchus, forming a relatively small mass at the hilus of the lung The fibrosis and shrinkage of pulmonary tissue were due to radiation therapy rather than to the neoplasm, culminating in the mutilation of the bronchi and blood vessels

As in other cases of this group the clinical manifestations of megalia cutis et ossium preceded those of the malignant new growth As in the other cases, too, this aspect of the disease was merely recorded but otherwise disregarded The opinion was expressed that the woman had myxedema in addition to her pulmonary cancer At necropsy one adrenal and the thyroid showed sizeable adenomas the pituitary showed hyperplasia of the oxyphilic cells

Case 37 *History* A manual laborer, 41 years of age, was admitted to [illegible] Hospital in March 1937 His father, a sufferer from [illegible] patient

step-

brothers and stepsisters were in good health

The onset of illness dated back to the latter part of 1935 It started with painful swelling involving successively the ankles knees upper extremities and shoulder joints From April to October 1936 he was under observation successively in three hospitals The report of the diagnosis in the first hospital (October 1936) reads as follows

The lungs and the heart showed no abnormalities The upper extremities showed limitation of and pain in all joints on motion The wrists and elbows were swollen and warm The hands were considerably enlarged and swollen as were the proximal interphalangeal joints The knees ankles and feet too were hot and tender on motion motion was limited The feet were considerably enlarged There was marked swelling of the breast Bronchoscopic examination failed to reveal abnormalities but an aspiration biopsy of the lung revealed tumor tissue which suggested metastatic carcinoma The Wassermann and Kahn reactions were negative and the exudate from the joints showed no abnormalities The patient was discharged from the hospital after two and one half months Two weeks later he was readmitted to the same institution In the interval he had gained 2 kg in weight but a productive cough small hemoptyses and dull pain in the right hemithorax had developed Pain in the knee joints became aggravated and their motion more restricted His temperature averaged 100 5 F His features were coarse his breasts were considerably enlarged and the extremities were *massive* *The pain in the joints was so severe that large* doses of sedatives were required to afford minimal relief In the right lung there was an area of dullness bronchovesicular breathing decreased vocal fremitus and moist rales were found anteriorly between the fourth and the sixth ribs On roentgen examination the shadow in the right lung visualized previously was now larger There was loss of normal tapering of fore arms The erythrocyte sedimentation rate was 55 per cent He was discharged and shortly afterward entered the Montefiore Hospital

Examination At Montefiore Hospital the following observations on admission were recorded There was evidence of considerable loss of weight The joints of the hands shoulders feet and knees were very markedly swollen and painful The lower limbs were massive clumsy and shapeless The tibias showed anterior bowing (fig 90) The hands were particularly striking resembling spades or paddles the fingers showing pronounced clubbing (figs 90 91) The joints of the knees and ankles contained small amounts of fluid There was general adenopathy and gynecomastia The lower two-thirds of the right lung were dull to percussion and the breath sounds in this area were barely audible His features were coarse and the color of the skin somewhat bronzed though not pigmented

Roentgen Examination of Bones There was an enormous periosteal reaction with bone production about the shafts of the femurs tibias fibulas and

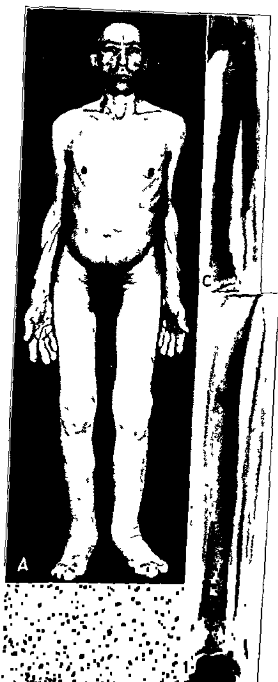


FIG 90 (Case 37) A, photograph of the patient, B, histologic structure of the bronchial cancer, C, roentgen appearance of the ulna and radius, D, tibia and fibula with extensive periosteal overgrowth

metacarpal bones There was extreme thickening and irregularity of the periosteum along the shafts of the humeri, ulnas, radiuses, tibias and fibulas (fig 90) In the pelvis there were hypertrophic changes along both iliums and femurs The sella turcica was large, but there were no evidences of destruction

Bronchoscopic Examination Bronchoscopic examination revealed a large friable mass completely occluding the bronchus of the lower lobe of the right lung below the apical branch

Diagnosis The clinical diagnosis was bronchiogenic carcinoma of the right lung, chronic pulmonary osteoarthropathy, endocrinopathy

Course The patient died after five months in the hospital

Necropsy The body was that of a well developed and moderately emaciated man The features were coarse, and the mandibulum was prognathic The hands were spadelike, with sausage like, clubbed fingers The left tibia was slightly curved anteriorly and thicker than the right Both were extremely swollen and shapeless, showing however an insignificant degree of edema The feet were large and flat, and the toes were clubbed The pleural cavities showed no fluid The pleura of the left lung was smooth and the lung showed no gross changes The right lung was adherent to the wall of the chest and the diaphragm The lower lobe of the lung was voluminous and firm A tumor measuring 8 cm in diameter and extending from the hilus was found in the midportion of the lobe Apparently it arose in the mucosa of a small bronchus and spread in a fanlike shape toward the periphery It was soft lobulated hemorrhagic and partly necrotic The large vessels and bronchi were patent The heart was of moderate size and the aorta of normal elasticity with a few plaques of atherosclerosis The coronary arteries were patent The liver was normal but the spleen was slightly enlarged and firmer than usual Other abdominal viscera showed no deviation from normal, except for the adrenals which showed several cortical adenomas The thyroid showed no abnormalities, but the anterior lobe of the pituitary was prominent The genitalia were normal on gross examination

Microscopically the tumor was made up of large polygonal cells with a sharply delimited clear cytoplasm and an eccentric nucleus rich in chromatin The cells were gathered in large nests separated by fine fibrous partitions containing small clefts filled with red cells (fig 90 B) Mitotic figures were common Necroses and hemorrhages were common throughout the new growth Areas of typical squamous carcinoma alternated with another type, described by some pathologists as paramalpighian In the metastases the new growth was diffusely of the paramalpighian variety Other viscera except for the spleen which showed amyloid were within normal limits The pituitary showed hypertrophy and hyperplasia of the eosinophilic cells of the anterior lobe

Comment Continental physicians di puted M arie s contention that the bones as well as the joints are involved in the proce s They were opposed to the term osteo*arthropathy* Although pathologic changes were not found

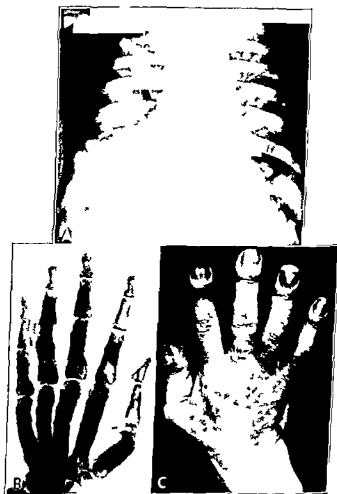


Fig 91 (Case 37) A carc noma of tl e lower l l e of the r ght lung B roentgen appearance f the left han l sho ing la nellar per ost t s C photogra h of the r ght hand with clubl ed fingers

in the joints of this patient clin cally tl ey all howed swelling exu l te an l exquisite sorene s

The osteoarthropathy in this case as in other cases cf tl is series man fested itself clinically before the pulmonary dise a e became evi lent Its

progress was rapid and stormy It was attributed to an endocrine disturbance the nature of which was not understood

The pulmonary circulation showed no deviation from the normal The adrenals showed several adenomas the thyroid was above the average weight the pituitary too was enlarged and under the microscope showed hyperplasia of the oxyphilic cells

Case 38 *History* A cabinet maker aged 55, entered the hospital complaining of severe pain in his right arm For twenty years he had been coughing particularly in the morning and evening but this did not interfere with his activities. In the summer of 1944 he became aware of an aching pain in his right shoulder soon followed by stiffness in the middle finger of the right hand Within the next six to eight months the pain increased in severity became nearly constant, extending upwards to axilla radiating down to the wrist and to the posterior aspect of the arm Stiffness of the fingers developed He entered a hospital where he remained three weeks and was discharged improved The improvement was however illusive and within a few weeks he was hospitalized at the Montefiore Hospital

Examination showed evidence of recent loss of weight He hiccoughed persistently His face was deeply wrinkled his appearance was sallow and his features were coarse acromegalic The tongue was enlarged The hands were large, broad and spade like the fingers showed a marked degree of clubbing The feet, too were large broad and cyanotic showing advanced clubbing of toes Both breasts were considerably enlarged the right twice that of the left they were movable lobulated and painless The right breast began to increase in size about two years the left about six months prior to admission (fig 92) There was no edema

The respiratory excursions of the right hemithorax were virtually nil tactile fremitus and breath sounds on this side were markedly diminished the percussion tone was flat to dull There was a respiratory wheeze audible throughout the upper half of the thorax The left lung showed no abnormalities

Roentgenologic examination revealed a dense shadow in the right upper thorax measuring about 6 cm in diameter Another density was noticed in the fifth interspace The 2nd rib was destroyed anteriorly The lower mandible was prognathic There was a marked periosteal thickening along the shafts of both ulnae right radius right fibula left tibia and left fibula The Wassermann reaction was positive The urine and blood showed the presence of glucose An insulin resistance test suggested the diabetes to be of pituitary origin

The clinical diagnosis was Bronchogenic carcinoma pituitary eosinophilic adenoma gynecomastia diabetes mellitus and osteoarthropathy

Necropsy revealed a squamous cell carcinoma to the right bronchus of the upper lobe with extension to the soft tissues and chest wall, metastatic

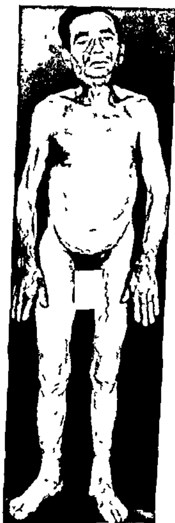


Fig 92 (Case 38) Photograph of the patient a few months before death

to the hilus and tracheobronchial lymph nodes The thyroid contained multiple colloid adenomas

Comment The appearance of the patient (fig 92) and the skeletal changes closely resembled the previous case An additional endocrinologic symp-

tom in this patient was diabetes which developed simultaneously with gynecomastia during the course of his pulmonary affection The insulin resistance test suggested the diabetes to be of pituitary origin

COMMENT

An analysis of the preceding cases revealed data pointing toward the conception that the hypertrophic pulmonary osteoarthropathy resulted from a disturbance in the function of the organs of internal secretion Summarily the data are in case 34 acromegalic appearance of the patient tufting of the terminal phalanges of the fingers and toes splanchnomegaly atrophy of the testicles and a large *adenohypophysis showing pronounced hyperplasia of* eosinophilic elements In case 35 acromegalic appearance of the patient bulldog scalp hirsutism macroglossia tufting of the terminal phalanges of the fingers and toes and thickening of cranial vault In case 36 mongoloid features of the patient secondary male characteristics large cortical adenoma of the adrenals several adenomas of the thyroid and hyperplasia of cells of the anterior lobe of the pituitary with eosinophilic cells in the majority In case 37 *coarse acromegalic features* gynecomastia several cortical adenomas of the adrenals roentgenologic evidence of enlargement of the sella turcica and tufting of the terminal phalanges of the fingers and toes In case 38 acromegalic features macroglossia gynecomastia and diabetes mellitus (pituitary)

That the lungs perform functions in addition to respiration has been stressed on many occasions Various writers have attributed to the lungs a role in the metabolism of lipids This was suggested by the fact that absorbed albumins and carbohydrates pass directly into the liver while fatty substances are transported by way of the lymphatics and the thoracic duct to the right side of the heart and to the lungs Fort in 1867 suggested that the lungs are characteristically secretory organs and he used the term *la glande pulmonaire*—the pulmonary gland In recent years Roger and his associates Aschoff and others have subscribed to this conception

Apparently the functions of the lungs are multiple and their interrelation with other organs particularly of internal secretion is complex and worthy of further study

As to the interdependence of tumors of the lungs and the organs of internal secretion no information is available to my knowledge

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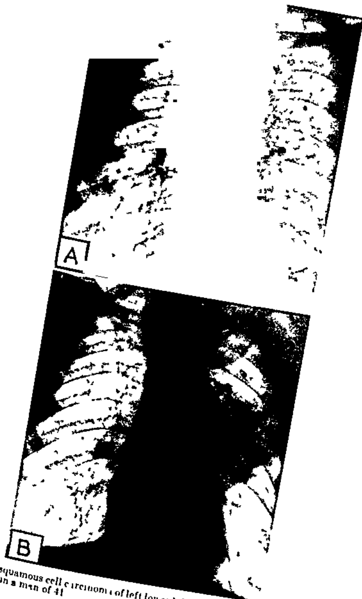


FIG 93 A squamous cell carcinoma of left lower lobe in a man of 70 B squamous cell carcinoma in a man of 41

Chapter IX

LABORATORY METHODS OF DIAGNOSIS

ROENTGEN RAYS

In moderately or far advanced cases of bronchiogenic carcinoma the roentgen rays usually play a confirmatory role but in the early stages their role is that of detection par excellence. The detection of the cancer at this juncture is not a simple procedure. Like the clinical, the roentgen appearance is pleomorphic (figs 93, 94, 95). The aim of the roentgenologist is to locate the tumor and to discern the state of the bronchus. The study is based essentially on the modern conception of the pathology of carcinoma of the lung which assumes that the disease arises in the wall of the bronchus wherefrom it spreads toward the pulmonary parenchyma.

The tumor is seen as a dense shadow at the hilus with or without a ragged infiltrating border. It may be seen in the middle of the pulmonary field, at the base or at the apex, occupying an entire lobe (lobar or massive type) or only a part, assuming a nodular or a miliary aspect. While some cancers maintain their "shape" throughout, others change it, and as Ross Golden put it, "the impression produced on the mind of the observer may be quite different at different stages of the disease."

The visualization of the bronchus with the roentgen rays requires a contrast medium. The pathologic aspect of bronchostenosis caused by cancer was detailed in another section. From roentgenologic point of view the obstruction of the bronchial lumen by malignant disease is characterized. Rigler depicted two aspects: one in the bronchial wall, cup shaped, with the walls of the bronchus extending around the neoplasm. Another, a marginal jagged defect within the outline of the contrast medium similar to that seen in carcinoma of the stomach. Not infrequently the terminal portion of the bronchus is seen frayed out, elongated and narrow, forming a "rat tail" deformity.

Early changes in the parenchyma of the lung resulting from stenosis of the bronchus consist in (obstructive) emphysema and atelectasis. *Fluoroscopy* and films taken in inspiration and expiration often demonstrate the presence of these conditions. Obstructive emphysema is best demonstrated in the expiratory phase.

In stenosing bronchiogenic carcinoma there occurs early, according to observers, an inspiratory displacement of the mediastinal structures *to the* side of the chest on which the lesion is situated. It is to be *noted, however* that as a result of metastases in the mediastinal lymph nodes, the trachea

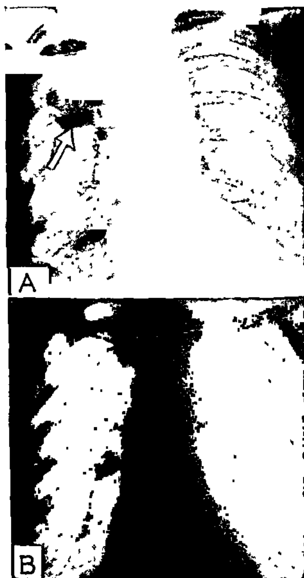


Fig 94 A undifferentiated cell carcinoma of right upper lobe in a man of 52 with widespread metastases (adrenals, bones and kidneys) B squamous cell carcinoma of left upper lobe in a man of 56 with widespread metastases (adrenals, bones, liver, thyroid)

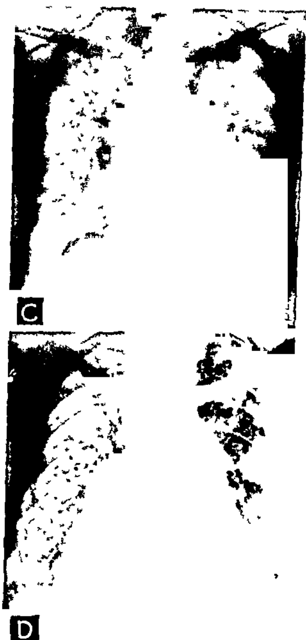


Fig. 93 (cont.) C Round cell carcinoma of left upper lobe in a man of 54. Bilateral tuberculosis. D Adeno carcinoma of left lower lobe in a woman of 72. The round nodule in the left lung is a metastasis.

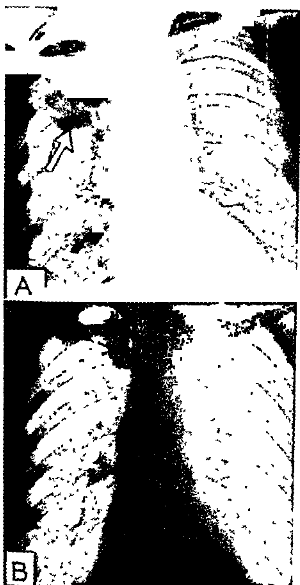


Fig 91 A, undifferentiated cell carcinoma of right upper lobe in a man of 52 with widespread metastases (adrenals bones and kidneys B squamous cell carcinoma of left upper lobe in a man of 56 with widespread metastases (adrenals, bones, liver, thyroid)

and at times the esophagus may be fixed or displaced to the opposite side of the thorax (Lenk)

Arce described a *radiologic sign observed* by comparing radiographic images before and after the establishment of pneumothorax In the roentgenograms obtained after pneumothorax it is noted according to Arce that pulmonary tumors undergo double displacement both vertical and horizontal, in the direction of the hilus When on comparing the roentgenograms one sees that the tumor shadow has not undergone any displacement it may be affirmed that the tumor is extrapulmonary and the finding is negative

Roentgenologic diagnosis of bronchial neoplasms has been advanced with the introduction of the method of planigraphy or tomography which aims at the delineation of a certain plane By using this method one is able to better visualize the bronchial tree and to sharper delineate the stenosis of the bronchus This method is particularly helpful in cases in which bronchography is not feasible and the tumor is beyond the reach of the bronchoscope

Tomography is believed to be of particular aid in the differential diagnosis between carcinoma adenoma and abscess of the lung The method is new and awaits further trial particularly in the detection of incipient tumors Friman Dahl affirmed that it is superior to other methods while Rigler pointed out that it serves as a supplement to or substitute for bronchography It should not according to the latter author be resorted to before bronchography or bronchoscopy

However that may be the roentgen rays are one of the most essential methods in the diagnosis of tumors of the thoracic cage A competent roentgenologist will as a rule establish whether one is dealing with an inflammatory or neoplastic disease he will ascertain whether the process originated within the lung he likewise will define the extent of the disease the effect of applied therapy, and the rate of progress of the tumor

BRONCHOSCOPY

The purpose of a bronchoscopic examination is (a) to ascertain the presence of tumor (b) to localize it (c) to discover its extent (d) to remove tissue for microscopic study A biopsy is of the utmost importance from diagnostic and therapeutic points of view (fig 96)

With the bronchoscope one can establish whether the tumor is situated in the main the lobar, the proximal portion of a lobar bronchial subdivision or beyond the proximal segment of a bronchus of the 3rd order The bron

or not the tumor extended upwards

re than a palliation bronchoscopic

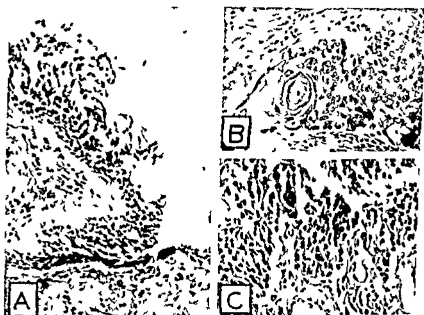
plugging the bronchus often leads to



FIG. 95. A, squamous cell carcinoma in a man of 72 with widespread metastases (adrenals, liver, spleen, omentum, pericardium). B, squamous cell carcinoma of right lower lobe in a man of 54, metastatic to regional lymph nodes.

reexpansion of the distal portion of the lung and promotes drainage thus preventing or suppressing an infection Bronchoscopy is of even greater value than bronchography in determining the early phases of an obstructive lesion of the bronchus It is carried out in a few minutes causing the patient relatively slight discomfort

In a study of 310 cases of bronchiogenic carcinoma from Chevalier Jackson's Clinic Norris found that tumors of the right and left main bronchi



yielded positive bronchoscopic results in 100 per cent of cases right and left lower bronchi respectively 88 6 and 86 4 per cent, right middle lobe bronchus 57 per cent and right and left upper bronchi 58 7 and 32 6 per cent respectively

ASPIRATION (NEEDLE) BIOPSY

By this method a needle of 17 or 18 gage calibre 15 to 20 cm in length is inserted through the chest directly into the tumor which is aspirated in the attached syringe by means of strong negative pressure It should not be confu ed with punch biopsy whereby tissue is nipped off and not aspirated The procured tissue is stained with the customary dyes and studied under the microscope (figs 97 98) Before proceeding with the aspiration, it is



Fig. [illegible]. Left bronchogenic carcinoma, [illegible] type. [illegible] obtained by aspiration from the case shown in A.

essential to ascertain the exact position of the tumor in the lung, particularly its depth, and also to establish the existence of an infection in the lung. When the pleural cavity is patent, there is danger of inducing an empyema. Air embolism and lung abscess have also been reported to have resulted from pulmonary puncture. The method is employed only when bron-

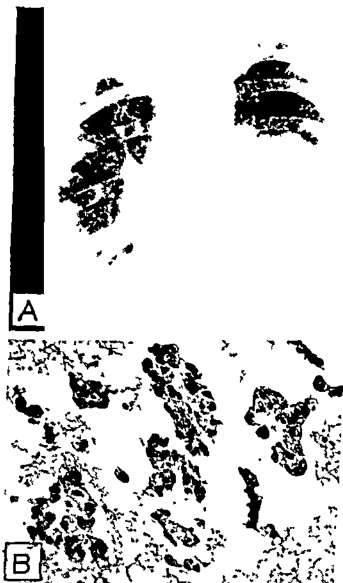


Fig 98 Cancer of the left lower lobe, biopsy obtained by aspiration from the tumor shown in A

choscopy is not feasible or when the tumor is inaccessible to the bronchoscope Opinion is widely divided as to the value of this procedure Some authors have stressed its potential dangers, such as infection of the pleural cavity, seeding of the tumor along the needle track, and air embolus Edwards warned that the removal of a piece of tumor for microscpic exami

nation by aspiration should never be carried out except in the diagnosis of tumor which should it prove to be carcinoma, would obviously be inoperable

Pleural Exudate

The incidence of a pleural effusion in bronchiogenic cancer varies with the stage of the disease It rarely occurs at the beginning of the disease while

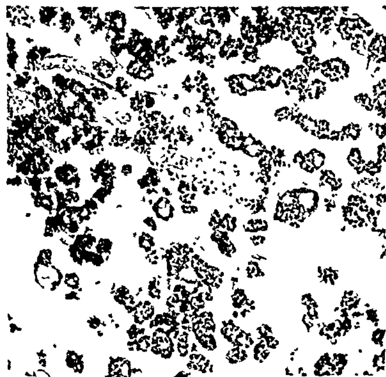


Fig. 99. Histologic structure of the sediment from a hemorrhagic pleural exudate in a case of bronchiogenic carcinoma

in the moderately and far advanced cases it is fairly common When an exudate is found in the pleural cavity it contains neoplastic cells in the [illegible] les as follows [illegible] ced in centri [illegible] fluid is then decanted and the remaining is centrifuged at a high speed Again, the supernatant fluid is poured off and the sediment is carefully remove placed on a piece of filter paper and fixed in a 5 per cent solution of fo

hyde or in Zenker fluid Paraffin blocks are then prepared cut and stained in the usual *manner*

Since Mandelbaum who was the first to introduce the method it has been practiced in most clinics with favorable results We have invariably obtained positive results in cases of bronchiogenic cancer Others have studied the exudate in metastatic cancer from the ovary breast pancreas kidney and gastro-intestinal tract

Chapman and Whalen in a study at the Boston City hospital stressed that *diagnoses of malignant neoplasms on the basis* of examination of cell blocks (prepared from centrifuged pleural exudate) were 94 per cent positive For a positive diagnosis (they stated) one should require the presence of fully or partly formed acini, or sheets composed of cells showing definite evidence of anaplasia

SPUTUM

Macroscopically the sputum of patients with bronchiogenic cancer is not pathognomonic except that it is often blood streaked However since the primary seat of the tumor is in the bronchial mucosa it is to be expected that bits of tumor will break off, or malignant cells will desquamate (exfoliate) and be expectorated (fig 100)

The idea of studying sputum for the presence of cancer cells belongs to Classe whose observation reported in 1890 passed unnoticed because of lack *of interest in carcinoma of the bronchus It has been revived in recent* years and at present it is claimed to be of great value in cases in which bronchoscopy and roentgenography yielded negative or doubtful results According to Gowar examination of the sputum by the smear method of Dudgeon is of value for the early diagnosis of cancer of the bronchus

The sputum should be expectorated in the morning so that there is no contamination with food particles Preservatives or disinfectants must not be added and the specimen should be examined as soon as possible after collection Specimens collected at bronchoscopy or coughed up shortly afterward are suitable for examination Dudgeon advised that the sputum be poured on an unglazed porcelain tile to concentrate it but Gowar found that by examining it in a large Petri dish on a black background it was easier to pick out portions best suitable for examination Blood streaked fragments or the more solid portions are picked out with a platinum loop or scalpel and are spread thinly on the slide

Several slides are prepared for each sputum They are fixed by immediate immersion in a bath of Schaudinn s solution for twenty minutes washed in 70 per cent alcohol containing a trace of iodine to remove excess mercury bichloride and then rinsed in distilled water The slides are stained with Mayer s hemalum, blued in tap water, counterstained with

eosin for two minutes dehydrated and mounted in Canada Balsam They are then examined with the low power of the microscope and suspected groups of cells are submitted to further study

Gowar used this method in 93 cases of suspected neoplasm of the lung In 64 3 per cent of the cases he succeeded in demonstrating malignant cells Cancer cells were found not only in advanced cases but also in a significant proportion of those in which the growth was still operable

The teaching of orthodox pathology was to the effect that individual cancer cells vary in no apparent way from normal somatic cells A diagnosis

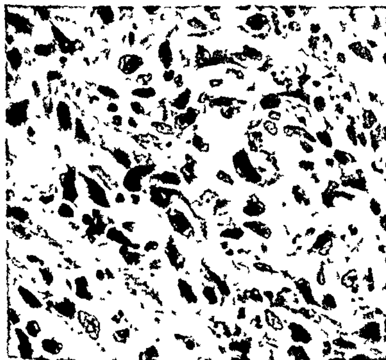


Fig 100 Histologic structure of tissue coughed up by a patient with primary carcinoma of the lung

of cancer was based chiefly on the cellular arrangement and of their ectopic location For instance, Chapman and Whalen in a recent study of serous fluid for evidence of malignant cells stressed that for a positive diagnosis one should require the presence of fully formed acini or sheets composed of cells showing definite evidence of anaplasia Adherents of the smear technic contradicted the old doctrine They stated according

to Papanicolaou that cancer cells though detached and completely isolated, as frequently seen in smears retain some distinctive traits which make possible their identification as an integral part of a neoplasm Papanicolaou who investigated this technic in gynecological cancer has lately reported on his success with this method in bronchiogenic cancer He wrote

Up to the present time (June 1946) our experimentation with sputum smears has covered 70 cases Of the 54 which have been completed and tabulated, 22 have been reported as positive for cancer on the basis of smears In 18 of these (82 per cent) the smear diagnosis was confirmed by biopsy or exploratory thoracotomy and in the remaining 4 (18 per cent) by X ray or other clinical methods The final diagnosis in the 18 confirmed cases was 7 bronchiogenic carcinomas 3 epidermoid carcinomas 2 metastatic, 1 adenocarcinoma of the right bronchus and 5 inoperable carcinomas of the lungs There was no case in which the smear was reported as conclusive for cancer which has been proved to be negative Seven cases have been reported as inconclusive but suspected on the strength of some *atypical cells present in the smears Of these 6 have been proved to be* positive by operation or biopsy and 1 remained suspected clinically In the group of 25 cases reported as negative on the basis of smears 3 (12 per cent) have been shown to present malignant neoplasms *of the lungs* 1 (4 per cent) remained obscure and 21 (84 per cent) have been finally diagnosed as negative In several instances the sputum smear furnished first evidence of the presence of a malignant neoplasm Some positive cases showed malignant cells in the sputum smears whereas bronchoscopy and aspiration biopsy were negative One of the patients had three successive aspiration biopsies which were negative The sputum smear was positive and showed several abnormal cells offering conclusive evidence of malignancy and slight metaplasia as reported A subsequent exploratory thoracotomy has shown an inoperable cancer of the lung [11]

Favorable results with this technic were reported by Dudgeon and Wrigley (68 per cent positive results) Althayzen (70 per cent) Wandel

[11] *Procedure* A specimen after coughing is requested This is fixed immediately

cent

(86 per cent), and the above quoted Papanicolaou. The findings were, however, contradicted by Herbut and Clerf on the following grounds: Fully half of their patients with bronchiogenic cancer had no expectoration of sputum until the disease had progressed to an incurable stage, and even with the aid of the bronchoscope they often failed to obtain enough secretion to make a single smear. When sputum was present it was usually so abundant and so dilute that a search for cancer cells became tedious and the results were disappointing. "The high figures given by investigators are hard to reconcile with our own," they wrote. They proposed instead a search of cancer cells in the bronchial secretion.

BRONCHIAL SECRETIONS

Technic. A bronchoscopic examination is performed in the usual manner and the secretions are secured from an area just proximal to the location of the suspected neoplasm. These are collected in an ordinary collector if the amount is copious, or in a special collector attached directly to the aspirator without an intermediate rubber tubing if the amount is scanty. When there is not enough secretion present to permit collection of even a drop, the aspirator may be washed with a drop or two of normal saline just enough to remove what secretion may be in the lumen, or smears may be made directly from the outer surface of the tip of the aspirator and fixed while still wet.

Smears are made as soon as possible. One may wait an hour or two so long as the material does not dry. Secretions poured into a Petri dish placed upon a contrasting background and with applicators those areas containing small sloughed particles or streaks of blood are picked off and transferred to slides.

Routinely six smears are made, but in equivocal cases the number is multiplied. A drop or two of secretion is placed near the top of the slide. This is covered with another slide and, with back and forth movement and firm pressure, the secretion is spread uniformly over each slide to a thickness of an ordinary blood smear. If pieces of tissue are present they have a tendency to slip peripherally, so that one must watch them closely to insure their being crushed and smeared properly.

The slides are then pulled apart, immediately dropped into a mixture of equal parts of 95 per cent of alcohol and ether, where they are allowed to fix for thirty minutes; they are then stained by the Papanicolaou method.[a]

[a] The staining is carried out as follows: (1) Fixed smears are rinsed in 70 per cent and 50 per cent alcohol and distilled water. Rinse three times in 0.5 aqueous solution of hydrochloric acid. Rinse in water. Differentiate for one minute in a solution of lithium carbonate (1 drop of saturated aqueous solution per 100 cc of water). Rinse thoroughly in water. (3) Rinse in distilled water, then in 50 per cent, 70 per cent, 80 per cent and 95 per cent alcohol. (4) Stain for one minute in OG6. (5) Rinse five times in each of two jars containing 95 per cent alcohol to remove excess stain. (6)

In 30 consecutive cases of bronchiogenic carcinoma 22 or 73 per cent showed the presence of tumor cells. As stated, Herbut and Clerf consider the examination of the bronchial secretion for tumor cells superior to that of the expectorated sputum. They believe that it "will aid in establishing an early definitive diagnosis, particularly in the tumors located at the periphery or in the upper lobes."



Fig. 101. Artificial pneumothorax in a case of carcinoma of the bronchus to the left upper lobe.

THORACOSCOPY

This method of diagnosis is resorted to in cases in which roentgenologic and bronchoscopic examinations failed to provide information. Direct

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... 6 ... times in each of three other jars con... ...lear in xylol for ten minutes

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Chapter X

TREATMENT

I RADIATION

Early Attempts Even before bronchiogenic cancer became an entity of clinical importance radiologists endeavored to treat it by radiation But their trials were disappointing Thus in 1925 Wood stated that the primary tumors of the lung have not done well (under radiation therapy) as a rule they seem to be very resistant and while some relief can be obtained it is not nearly as great as that often seen in metastatic masses"

For the past two decades attempts have been multiplied and at present roentgen therapy of primary carcinoma of the lung is widely practiced

Results Results obtained by a therapeutic measure in cancer should be gauged by (1) change in size of the new growth (or in its complete disappearance) as evidenced by physical and roentgen ray examinations, (2) lasting systemic improvement Temporary amelioration is misleading since cancer like most chronic diseases has natural remissions at which time the patient shows remarkable improvement (3) cure of the disease or at least a lengthened period of survival as a result of the applied therapy

The opinion of radiologists is to the effect that in a large number of cases roentgen ray therapy has yielded improvement and has prolonged life

Chandler and Potter found that in 59 patients treated the survival was eleven months following treatment while in the 41 untreated the average duration of life was six months

In 100 selected cases treated by Maxwell and Nicholson the average duration of life in the treated patients was 14 months and in the non treated 10 9 months Roberts found that in malignant disease of the lung x ray treatment if carried out intensively caused temporary regression of the primary tumor reexpansion of the collapsed lung and disappearance of enlarged cervical lymph nodes

Leddy and Moersch published a comparative study of 125 treated and 125 untreated patients Ninety nine of the treated were in the terminal stage when treatment was inaugurated and 102 received entirely insufficient x ray therapy Twenty five of the treated lived from one to twelve years one—twelve years 2 months one—ten years 7 months one—nine years 11 months the other twenty two lived from one to five years Of the second group none survived for longer than a year In the

opinion of these writers "roentgen therapy is an excellent method of palliation, it has produced so-called cures."

In a later report Leddy stated "In the greater portion of cases of malignant disease of the lung the patients are debilitated, past middle age, and, therefore, poor subjects for any form of intensive or radical treatment. Exceptionally, however one may observe a case in which the tumor is in an early stage of development and the patient is in good physical condition. In such a case, a cure or great improvement may reasonably be expected."

Craver analyzed the results obtained in the treatment of 142 patients with roentgen rays and of 14 treated by the radon or radium element pack. He noticed that as the tumor dose in roentgens increased in the initial cycle the duration of life following treatment increased. Patients receiving from 2,000 to 3,000 roentgens in the tumor survived an average of 8.2 months as compared with an average survival of only 4.3 months in those receiving less than 1,000 roentgens. Survival of five years was rare occurring in only 8.3 per cent. One of the treated patients survived 12.5 years, two over 4.5 years, one 3 years, one 2 years, one, 18 months, five, 6 months and eight less than 6 months. Roentgen radiation seemed to be more effective than external radiation by radium.

Pohle and Sims are emphatic as to the palliative value of cautiously applied x-ray therapy and recommend giving it a trial as long as the general condition of the patient permits. They too stress the fact that in most instances the disease was in an advanced stage when the patient came under the care of the radiotherapist. Twenty nine or 42 per cent of their patients had metastases when first seen.

Bloch and Bogardus, neither surgeons nor roentgenologists and not inclined by training toward either method of therapy, investigated the results obtained by roentgen ray therapy in 88 patients. The dose administered varied from 1,2000 to 16,000 roentgens. They found that the duration of life after the onset of symptoms in the patients who were treated was about the same as in the untreated patients, the mortality too was not diminished. Only three patients of the whole group noticed disappearance of symptoms which was due to a release of bronchial occlusion and clearing of atelectasis following some shrinkage of the tumor rather than to an essential destruction of the neoplasm. The evidence produced by these writers is to the effect that as a curative treatment roentgen therapy was a complete failure. Moreover the effects from irradiation with hard rays were considerable: nausea, abdominal distress, severe headaches, general weakness and malaise.

Radio-Sensitive and Radio Resistant Cancers. From the point of view of radiation therapy carcinomas are divided into radio-sensitive and radio-



FIG 102 (cont) C, fifteen months later, showing reappearance of the cancer in the hilus, D, one year later

amount ("dose") of radiation larger doses result in severe bronchopneumonia which never subsides. Three months after radiation the reaction is still present (infiltration with small and large mononuclear cells alterations in the bronchial epithelium fibrosis). Large doses induce exudative and fibrotic changes in the pleura (pleuropneumonitis).

Jacobsen studied the lung of a patient with bronchiogenic carcinoma who had received 15,000 roentgens over a period of nine years. The lung

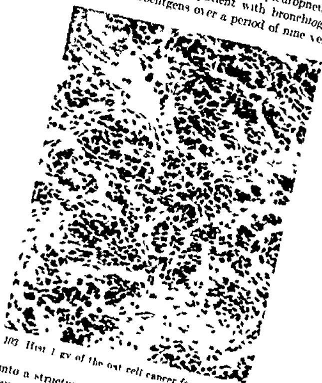


Fig. 103. Histology of the oat cell cancer found at autopsy

was converted into a structure of fibrous consistency the size of a man's fist and the pleura was thick and hard. Remaining nests of pulmonary tissue were atelectatic. A tumor nodule 2 cm. in diameter containing viable cells at the periphery was found embedded in the fibrosed tissue. Here then the roentgen rays were carcinocidal as well as pulmonocidal. It is significant that the huge dose of radiation failed to destroy completely the malignant cells which were probably protected by the densely fibrosed tissue.

A roentgenogram from a patient treated for left bronchiogenic cancer is shown in figure 102. From October 1927 to March 1929 he received

233,000 mc hrs from an element pack applied to the upper thorax There occurred a general improvement but locally a minute dense shadow could still be visualized 18 months later Two years later the cancer resumed its rapid growth At necropsy the entire upper lobe of the left lung was fibrosed and contained nests of cancer cells similar to those obtained by a bronchoscopic examination five years previously (fig 103)

Summary Although the prevailing type in bronchiogenic carcinoma is the radio-sensitive squamous epithelial cell treatment with radium or x rays has thus far yielded no favorable results The failure was probably due to many factors of which the following are outstanding

1 Tardy inauguration of treatment
2 Poor condition of the patient
3 Large size of the tumor
4 Infection of the lung
5 Lack of proper indications either in planning or in the execution of radiotherapy (Leddy)

II SURGERY

Progress in Thoracic Surgery The use of surgery in the treatment of intrathoracic malignant disease was widely expanded in the past decade largely as a result of the progress made in the methods of anesthesia and the introduction of antibiotics Like cancer of the abdominal viscera that of the bronchus is claimed to be essentially the sphere of the surgeon The success of Graham the first to remove a lung for bronchiogenic cancer (1933) stimulated others and at present surgeons throughout the country (and elsewhere) perform pneumonectomies for inflammatory as well as neoplastic conditions

Pneumonectomy for Bronchiogenic Cancer While the feasibility of pneumonectomy for carcinoma of the bronchus is no longer contested its application is thought by many to be limited since the early pre metastatic stages of the disease are still often overlooked Indeed when diagnosed its metastases are at times so widely distributed that removal of the primary tumor is obviously futile

In this respect carcinoma of the lung is comparable to cancer of other organs From 30 to 50 per cent of cases of cancer of the breast forty two per cent of cases of large intestine and 75 per cent of cases of the stomach were inoperable when first seen in the Mayo Clinic Sixty two per cent of the operable cancers of the breast 38 per cent of cancer of the large intestine and 53 per cent of cancer of the stomach had metastasized to regional lymph nodes when seen in the same clinic

As the problem stands the histologic structure and the macroscopic appearance of the cancer or its topography are of doubtful assistance in

foretelling its metastatic propensities. Nor are there convincing clinical criteria whereby one can ascertain whether metastases to visceral organs had already taken place. While metastatic involvement of the central nervous system or peripheral nerves (phrenic, recurrent laryngeal) yield symptoms at an early date, metastases to the liver, the adrenals and the bones respectively usually remain asymptomatic for a long time. This holds particularly true of the liver and the adrenals.

It is true that while metastases to the tributary lymph nodes are found at autopsy in from 90 to 98 per cent of cases, the viscera are involved less often (the liver in from 40 to 50 per cent, the bones and adrenals in about 40 per cent). But quite often irrefutable criteria are not available to separate tumors that have metastasized from those that have not.

The roentgenologic and physical examination provide insufficient criteria to indicate the feasibility of an operation. "I am perturbed by the large number of vain explorations that are performed in order to find a few cases that might be considered suitable for excision and I am sure that many of the cases explored today should never be put to the pain, disappointment and expense of surgery," wrote Shenstone. Ochsner and DeBakey stated: "Even in those cases which are considered suitable for exploration, the operability incidence is depressingly low." On the other hand, Rienhoff considered that "Surgical treatment of malignant tumors of the lung has been a boon to patients and a lively stimulus to clinicians interested in pulmonary lesions."

The seriousness of the problem was echoed at the Twenty-Fourth Annual Meeting of the American Association for Thoracic Surgery. Said Graham: "I look with a good deal of misgiving upon notes of pessimism about this subject (pneumonectomy for bronchiogenic cancer) which have been expressed this morning and also which I hear from time to time expressed by members of this organization, that is by those who are doing this work and who are actively interested in it."

Statistical Data. Churchill found that in 155 cases of bronchogenic cancer pneumonectomy appeared feasible in 52, or 33.6 per cent, but resection was possible in only 27, or 17.4 per cent.

Of 106 patients observed by Brock, only 13, or 12.3 per cent, were considered suitable for exploration. Nine of these were submitted to operation but only four were found operable, an inoperability of 96.2 per cent.

Harrington's series comprised thirty cases, of which 21 were found to be inoperable after exploration. Of the 9 on whom pneumonectomy was performed, 3 died of hemorrhage and respiratory and cardiac failure respectively, following the operation. Of the 6 that survived, one died three months later of an unknown cause and 5 lived from three to eight months.

Edwards reported that in 172 persons with cancer of the bronchus seen over a period of 30 months, 28 were subjected to an exploratory operation, only 13 survived a pneumonectomy, 6 lived more than six months

Ochsner and DeBakey collected 79 cases of total pneumonectomy for neoplastic diseases to which they have added 7 cases of their own Of 86 patients 55, or 63 per cent, died, and 31, or 36 per cent, recovered In 20 of the 86 cases, the type of neoplasm was not indicated, of the 66 remaining, 59 were carcinomas Of the 7 patients operated upon by Ochsner and DeBakey, 5 died and 2 recovered The causes of death of the 5 patients were, respectively, hemorrhage on the table, asphyxia one hour after the operation because of the tongue dropping back, severe tracheitis and pulmonary edema, cardiac failure, peritonitis from rupture of the intestine Of the 2 survivors, one is alive two and a half years after the operation, the other was operated shortly before the authors made their report and they considered it too soon to draw conclusions concerning the outcome

Jones related that of 196 cases of bronchiogenic cancer observed by him in four years, only 39 per cent were clinically operable, and when exploration in 66 cases of this group was done only 39 (59 per cent of 66, 20 per cent of 196) were operable and had pneumonectomy Of these patients, 2 (5 per cent of 39) died in the hospital, and 11 (29 5 per cent of 37) died later Twenty six patients (70 5 per cent of 37) remained alive, and a number of these will probably die of recurrence or metastases Jones stressed the "appallingly low operability and curability" of carcinoma of the bronchus In accord with observations made by others he pointed out that an otherwise fatal disease, curable with a 5 per cent mortality rate, is a challenge to the profession to make a diagnosis earlier "

Of 71 persons on whom pneumonectomy for bronchiogenic cancer was performed by Rienhoff, 15, or 21 per cent died in the hospital Among those who survived 3 lived seven years, 1, nine years, and 1, eleven years—all restored to normal activity in every respect " Rienhoff pointed out that the mortality rate of 20 to 30 per cent should be looked on as high but that 'it is reasonable to expect a substantial reduction in the future "

From 1939 to 1944 Graham performed 77 pneumonectomies for primary [illegible]

years 8 months, 5 years 5 months, and 4 years 6 months According to him the possibility of a permanent cure seems to be definitely established He stresses that the main task consists in the education of the medical profes

sion in the early diagnosis of the disease and in persuading those who first see these patients to refer them promptly to a competent thoracic surgeon One should dispel (affirms Graham) the all too common idea that the operation of total pneumonectomy for bronchiogenic carcinoma carries with it an enormous operative risk

Contraindications Age per se is not a contraindication provided the general and the cardio vascular status of the patient are good However, pneumonectomy should not be attempted in instances when the pleural exudate is hemorrhagic the corresponding half of the diaphragm is paralyzed, the left vocal cord is paralyzed (in left sided cancer), there is pain in the thoracic wall or down the arm Finally, when there is bronchoscopic evidence of extention of the tumor into the trachea or evidence of the presence of metastases to distant organs

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BRONCHIOGENIC ADENOMA

Chapter XI

BRONCHIOGENIC ADENOMA

The lungs are the seat of a variety of tumors originating from epithelial tissues, connective tissues, cartilage and vascular elements. Fibromas, chondromas, hemangiomas, rhabdomyomas and lipomas have been observed. These tumors occur with great rarity and are of limited clinical significance.

There is one variety of epithelial tumor originating in the wall of the bronchus which is of great importance from the clinical and pathologic standpoint.

NOMENCLATURE

This has been reported under various names: Polypoid adenoma, vascular adenoma, solid adenoma, cylindroma, bronchial adenoma, adenoma of bronchial mucous glands, mixed tumor of the lungs, carcinoid and basal cell carcinoma of the bronchus. In most instances, however, it has been referred to as bronchial or polypoid adenoma.

HISTORICAL

Laennec mentioned the tumor for the first time in his treatise on Auscultation. He wrote:

> It is rare for polypoid excrescences to develop on the mucous membrane of the bronchi; only three examples are known to me. It seems that these excrescences are of the type of vesicular polyps of the nose, ear and uterine cervix; that is to say, they are formed by tissues analogous to the mucous membrane containing small serous cysts.

Polypoid adenoma remained unknown or unrecorded until 1882, when Mueller found a case accidentally at the postmortem examination of a patient who had died of a purulent infection of the lungs. Again it remained unheeded until the end of World War I. It is noteworthy that a lesion which catches the eye should have been overlooked. Chiefly American and British physicians are responsible for the interest evinced in this "new disease."

Yankauer described a case in 1922 and another in 1929. He treated bronchoscopically a polypoid adenoma in a man of 30 who, following an attack of pneumonia, developed a stubborn pain in the right side of his chest. The patient was subjected to phrenicectomy with some relief from

pain but not from cough Bronchoscopy revealed a grayish, pedunculated neoplasm occluding the bronchus of the right middle lobe, which was removed with relief of symptoms

A search of the available literature by Patterson revealed that up to 1930 twenty six cases of this type of tumor had been recorded Of these, 10 had been diagnosed postmortem and the remaining 16 during life In a series of 150 cases of bronchial tumors Morlock and Pinchin found 6 per cent adenomas Kramer and Som found 6 per cent (23 adenomas) among 353 cases of bronchial tumors Pollack, Cohen and Gnassi found 51 adenomas in a series of 104 benign bronchial tumors recorded in the literature Of 243 cases of tumors of the lungs studied bronchoscopically in fifteen years, Clerf and Bucher observed adenomas in 12 per cent of cases Churchill stated that the ratio of bronchiogenic adenomas to bronchiogenic carcinomas not proved microscopically is 1 20 and the ratio to bronchiogenic carcinomas proved microscopically is 1 10 It was estimated that adenoma is the commonest benign bronchial tumor

HISTOGENESIS

Adenoma originates in the mucosa of a bronchus The notion that it invariably starts in the larger bronchi has recently been contradicted Bronchi of smaller size, too, are susceptible The origin of the tumor has been traced by some observers to the cells lining the mucous glands of the bronchial mucosa by others to the cells lining the excretory ducts of these glands by still others to so called oncocytes, epithelial cells resembling those of the organ in which they are found and differing from them in size and in the presence of cytoplasmic acidophilic granules and deeply stained pycnotic nuclei Womack and Graham have stated that bronchiogenic adenomas originate in anlages that have failed to develop normally They stated These tumors resemble fetal pulmonary tissue they result from the failure of embryonal bronchial buds to develop into normal (bronchial) structures' In their opinion there exists a similarity of behavior and in some respects of origin of bronchial adenomas to the mixed tumors of the parotid gland and as such the bronchial tumors were designated by them as mixed tumors of the lungs

There are two possible sources for the origin of the bronchial adenomas (1) The bronchial mucous glands (2) The basal cells of the bronchial mucous membrane

When the mucous glands are involved the tumor cells resemble the secreting cells of the gland—large polygonal cells with a wide rim of cytoplasm containing acidophilic granules and deeply stained nuclei A case of this variety is herein presented

ILLUSTRATIVE CASE

Case 39 *History* The past history of the patient aged fifty seven, was irrelevant, and his present illness was that of hypertention and hypertensive cardiac disease to which he succumbed At necropsy the adenoma was found in the lower part of the left bronchus at the point of its division into the upper and lower branches It represented a round smooth, grayish polypoid elevation protruding into the bronchial lumen constricted at the base (fig 104) It measured 1 cm in diameter It was composed of clus



Fig 104 (Case 39) A polypoid endobronchial adenoma protruding into the bronchial lumen (arrow) B cut surface of the tumor lined by a papilla forming metaplastic epithelium C to the adipose tissue extending from the submucosa

ters of alveoli made up of large polygonal cells (fig 105 C and D) The similarity of these cells to the aforementioned oncocytes is noteworthy The tumor was surrounded by a collagenous capsule covered with bronchial epithelium undergoing metaplastic transformation

In this case the polypoid excrescence to use Laennec s term took origin in the cells of the mucous glands However more frequent source for the genesis of these tumors are the basal cells of the bronchial mucosa These cells found in clusters interspersed between the columnar and the mucous (goblet) cells represent a dynamic unit playing a role in regenerative and fibrogenic processes taking place in the lung (fig 106) This cell

as detailed in Chapter II, is also the mother cell for bronchiogenic carcinoma

PATHOLOGIC ANATOMY

Early observers entertained the notion that the tumor invariably advances toward the bronchial lumen leaving the parenchyma of the lung intact This has been contradicted by recent observers who found that in the majority of cases it progresses in two directions—toward the lumen of



Fig 105 (Case 39) C photomicrograph showing the structure of the tumor surrounded by loose connective tissue covered by metaplastic epithelium D high magnification of section shown in C

the bronchus and toward the parenchyma of the lung In its bidirectional advance it ultimately forms a pouch divided by a constriction at the point of its origin in the wall of the bronchus assuming a somewhat hour glass shape In the course of its expansion it may engulf and destroy the bronchus and appear as a round well demarcated growth often surrounded by a fibrous capsule

At first the endobronchial segment of the adenoma appears as a wart like prominence usually firm and sessile (fig 104A) in the advanced stages it becomes pedunculated sometimes assuming a pyriform shape suspended and hanging by its constricted neck like the clapper of a bell Its tendency

to project upwards is due to the expulsive effort of coughing. The part of the tumor protruding into the bronchial lumen is covered by bronchial epithelium which has undergone metaplastic changes. Contrary to the behavior of bronchiogenic carcinoma which destroys the bronchial mucosa at the outset, bronchiogenic adenoma merely pushes the mucous membrane



Fig 106 Photomicrograph showing an early stage of proliferation of basal cells of the bronchial mucosa; some cells are in mitosis

which becomes metaplastic, as a result of circulatory and inflammatory disturbances (fig 105 C).

Some observers described an intramural type of adenoma, said to be strictly confined to the bronchial wall wherein it expands.

HISTOLOGIC STRUCTURE

Microscopically the adenoma is remarkably pleomorphic, which explains the multiplicity of names given it. The structure most commonly observed

is reproduced in fig 108B The cells are uniformly the size of a lymphocyte or a plasma cell with a somewhat oval nucleus and a narrow rim of cytoplasm *The arrangement* of the cells is orderly usually forming tubules without lumens The stroma is delicate containing occasional slits lined by endothelial like cells In advanced cases the stroma becomes dense undergoing calcification and ossification

Of all forms the so called cylindroma is probably *the most important* It, too forms tubules but they are filled with mucous or cylinders of tumor cells and mucoid or hyalin secretion (Swiss cheese pattern) Bronchial *cylindromas resemble mixed tumors of the salivary gland*

RATE OF GROWTH

Early observers considered bronchiogenic adenoma a slow growing benign newgrowth The opinion of recent investigators is divided between those who stated that (1) it is a benign neoplasm and (2) those who considered it potentially malignant

1 Bronchial adenoma is a benign tumor

These tumors are slowly growing they do not metastasize and they do not have any inherent tendency to become malignant The contrary impression has been due to confusion and error in histopathologic diagnosis (Jackson and Konzelmann)

Bronchial adenona may be regarded reasonably as a benign growth which does not cause death by direct or metastatic extention (Foster Carter)

Bronchial adenoma is an epithelial tumor that is probably benign and non metastasizing (Clerf and Bucher)

Cases of bronchial adenoma with meta tases were probably not cases of adenoma originally (Brunn and Goldman)

We have not yet had evidence to support the theory that bronchial adenoma is a malignant tumor (R Adams)

2 Bronchial adenoma is a potentially malignant tumor

The endobronchial tumors (adenomas) are characterized by a long clinical course with low grade but very definite malignant manifestations *(Adams Steiner and Bloch)*

Bronchial adenoma grows slowly but shows definite invasiveness (through the bronchial wall) lack of orderly structure and a strong tendency to recur after local removal In other words there is evidence of *local* malignancy (Lowry and Rigler)

The majority of these tumors became malignant After they have developed full flown features of malignancy the identity of the original tumor is lost (Graham and Womack)

Adams and his associates found in one of their cases a metastasis in the vertebral bone marrow, in another, in the tracheo-bronchial lymph node and in still another in a mediastinal lymph node and the liver. In Anderson's case, tumor cells extended between the bronchial cartilages and involved the entire thickness of the bronchial wall; they were found in several perivascular and peribronchial lymphatics. Holley in a review of 38 cases, found one that extended into the capsule of the node, two that had invaded a hilus lymph node, one that invaded small vessels and one that metastasized to the liver. Laff and Neubuerger reported a cylindroma which had metastasized to the opposite lung. Tinney and McDonald found extension of the tumor within the bronchial wall in 13 of 15 cases; in two, tumor was found in the regional lymph node.

The occurrence of metastases, while very rare, is nevertheless puzzling because the histological structure of the adenoma is that of a benign tumor. It is significant that the metastases were minute, sometimes microscopic, and confined to only one or two organs, and they occurred in persons whose disease was of many years duration. In cancer it has been noticed metastases often occur in inverse ratio to the tempo of the growth; the slower the growth the more widespread are the metastases.

Indeed, the factors which characterize malignancy, namely recurrence of growth after removal, metastases, radiosensitivity and constitutional symptoms were lacking in bronchiogenic adenoma. The disease ran a course of many years and the metastases found in one or two organs were minute and few and were discovered accidentally at the postmortem examination. After the complete removal of the tumor the patient recovered.

At the Massachusetts General Hospital, of 175 cases of bronchial neoplasms bronchial adenomas were found in 17 or 10 per cent. Fifteen (88 per cent) of the 17 were living and asymptomatic from three to five years later. Of 155 patients with carcinoma of the bronchus only 5 or 3 per cent were alive for the same period. Of 28 patients in whom carcinoma has been removed surgically only 3 (11 per cent) have a chance of five years survival, while of the 11 patients in whom the adenoma had been removed surgically 10 (90 per cent) were living and none revealed signs of malignant disease.

DIAGNOSIS

Asymptomatic Adenoma. Bronchiogenic adenoma has been compared with an iceberg since only part of it is visible on the surface and like an iceberg its advance is extremely slow. Cases are on record in which symptoms existed for decades. That there is a preclinical asymptomatic period goes without saying. There are also cases which remain asymptomatic from cradle to grave.

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ILLUSTRATIVE CASE

Case 40 History A married woman, aged *sixty four, was admitted to* the hospital with the diagnosis of congestive heart failure She had been in good health until she was 48, when diabetes hypertention and hypertensive cardio-vascular disease developed Signs of congestive heart failure appeared 12 years later, at the age of 60

With the roentgen rays the lungs showed congestion, the left diaphragm was depressed and the right costophrenic angle was obliterated, the pulmonary artery on the right was almost twice the normal width

A round sharply circumscribed area of density measuring about 1 5 cm in diameter was found in the middle zone of the right lung at the level of the third interspace anteriorly (fig 107 B) It resembled a metastasis or a bronchiogenic carcinoma The patient died of acute cardiac failure and uremic acidosis

At necropsy the lungs showed no atelectatic or inflammatory areas At the base of the right upper lobe lateral and slightly posterior to the hilus, an encapsulated tumor measuring 2 cm in diameter was found (fig 107 A) It lay approximately midway between the anterior and posterior surfaces closer to the hilus than to the surface involving the secondary branch of a bronchus to the upper lobe The trachea and the tracheo bronchial lymph nodes were normal The lung contained an azygos lobe

On histologic examination the tumor seemed to arise in the submucosa of a small bronchiole It was sharply demarcated and was composed of *polyhedral cells of uniform size and shape containing a wide eosinophilic* cytoplasm and a large round or oval nucleus (fig 107 C) In some areas the structure was papillary in others the cells grew in anastomosing cords, *and in still others in solid sheets In places there was the suggestion of a* glandular pattern The vascularity was moderate and at the periphery fibrosis and calcification were conspicuous

Comment The solid benign adenoma which originated in a small bronchiole was asymptomatic and was discovered by accident Of five patients reported by Maier thoracic symptoms were present in two while in the re*maining three the adenoma was discovered accidentally* in one during a roentgen study of the gastro intestinal tract and in two during an x ray survey

Early Symptoms Early complaints are usually those of cough productive of mucoid sputum occasionally streaked with blood The ominous symptom however is the occurrence of hemoptysis which is characterized by abruptness and copiousness *Carcinoma of the lung* too produces hemorrhages but they are rarely abundant The source of the bleeding has been

traced to ruptured thin walled blood vessels which abound in polypoid adenomas In the performance of biopsies it has been noticed that, unlike

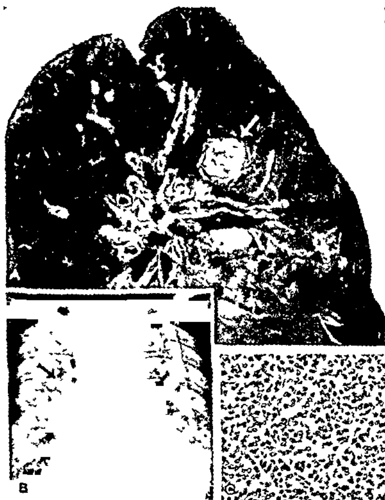


Fig 107 (Case 40) A cut surface of the lung showing the well circumscribed adenoma (arrow) B roentgenologic appearance of the tumor (arrow) C histologic structure

bronchiogenic carcinoma adenomas bleed profusely the bleeding reaching at times a dangerous point

Further in its course the symptomatology is dominated by the increasing

size of the endobronchial growth causing occlusion of the bronchial lumen It is well to consider two phases

(1) Preobstructive or partially obstructive

(2) Obstructive

In the first phase in addition to cough and bleeding a wheeze in the chest is heard (heard best with the patient's mouth open) often by the patient himself Not infrequently there is a soreness of the chest on the side of the affected bronchus *Although not completely shut off from ingress of* air the lung loses its usual resistance and readily becomes a prey to infection the patient suffers sporadically from colds with elevation of temperature (recurrent pneumonia)

Bronchostenosis Bronchial stenosis whether caused by a tuberculous infection or a malignant or benign neoplasm induces stagnation in the lungs with the formation of a thick mucopurulent secretion The bouts of fever lasting as long as this condition persists are usually due to the obstruction When the plug is removed spontaneously or with the bronchoscope the condition clears up only to recur with another obstructive episode hence the recurrent pneumonic attacks

When the obstruction becomes permanent the segment of the lung distal to it becomes atelectatic and infected with pyogens inducing pneumonitis bronchiectasis abscess and empyema

Bronchostenosis and bronchial obstruction were first recognized ten to fifteen years Older clinicians (as well as pathologists) unaware of this phenomenon focused attention on parenchyma of the lung which they treated without effect Patients usually succumbed to complications Indeed early recognition of the source of the trouble followed by proper therapy is life saving

Site Adenoma has a tendency to involve bronchi of all sizes but in most instances they were found in bronchi of I II and III order From a series of collected cases it would appear that it is encountered oftener on the right side Of 217 cases from the literature it occurred on the right side in 127 or 58 5 per cent and on the left in 90 41 5 per cent The lower lobe seems to be affected more often than the upper

Age The highest incidence of the disease is observed in the third and fourth decades but other age periods are not immune Maier removed an adenoma from a Negro girl aged 16 Kramer and Som observed an adenoma in a boy of 13 but 61 per cent of their patients were between the ages *of 21 and 38* *Jones and his associates reported a case of an adenoma of the* right main bronchus in a boy of 10 years The boy died during a bronchoscopic examination

Of 123 cases culled from the literature 109 affected persons were under 50 and only 13 above that age *It may be observed that bronchiogenic*

adenoma is rarely seen at the age period when bronchiogenic carcinoma occurs most frequently

Sex Of interest in this connection is the sex incidence Of 160 cases 71, or 44 25 per cent, occurred in men, and 89 or 55 75 per cent, occurred in women These figures are of particular significance when compared with those found in bronchiogenic carcinoma—80 per cent in men and only 20 per cent in women

BRONCHOSCOPY

In the introductory paragraphs it was stated that the tumor has the aspect of a pouch constricted in the middle in an hourglass fashion at the point of constriction it is astride on the bronchial wall one segment advancing toward the lung and the other toward the bronchial lumen The adenoma has also been likened to an iceberg one segment of which (endobronchial) is on the surface while the other (intrapulmonary) is submerged It is thus apparent, that while the bronchoscopist is not in a position to ascertain the extent of the lesion he is able to point out the diagnosis and remove tissue for microscopic study

TABLE 19

Salient Diagnostic Features

AGE	SEX	SITE	CLINICAL MANIFESTATIONS		
			First Phase	Second Phase	Third Phase
80 to 85 per cent under forty	Over 60 per cent in the female	About 60 per cent on the right	Dry or moderately productive cough occasional streaking of sputum with blood	Cough hemoptysis wheeze in chest recurrent colds pneumonia with pyrexia pain in chest	Atelectasis of lung distal to obstruction pneumonitis bronchiectasis putrid abscess empyema constitutional symptoms

Bronchiogenic adenoma, by its polypoid and smooth appearance and its readily and copiously bleeding surface is entirely unlike bronchiogenic carcinoma The wall of the affected bronchus in carcinoma is thoroughly permeated by *tumor it is stiff and frozen* as is often the entire mediastinum In adenoma however the bronchial wall retains most of its elasticity the mucosa is hyperemic or gray showing metaplasia

With the bronchoscope one is able to ascertain whether the tumor is sessile or pedunculated also the degree of bronchial occlusion The bronchoscopist is also in a position to remove the mucous occluding the

bronchial lumen, thus facilitating reaeration of the atelectatic portion of the lung

Tissue removed for histologic study should be studied with the utmost care, for it is known that isolated sections may show features not unlike those of carcinoma In the past, cases of benign adenoma have been erroneously diagnosed as polypoid bronchiogenic carcinoma and allegedly cured by local treatment

ROENTGENOGRAPHY

Modern methods of bronchography with the use of an opaque substance reveal the cup shaped irregularity of the bronchial wall and the location of the intrabronchial growth The round adenoma with its smooth surface produces a defect *sui generis* easily distinguishable from the defect seen in bronchiogenic carcinoma

By the use of tomography the early direct diagnosis is possible The intrapulmonary newgrowth is visualized as a round dense shadow with well defined borders, characteristic of benign tumors

TREATMENT

With the advent of the modern concept of bronchiogenic adenoma notions of its treatment have undergone changes One no longer considers that the treatment of the visible segment of the adenoma is sufficient alone to cure the disease Literature is replete with instances where the protracted local therapy with radium forceps, electrocoagulation or aspiration have failed to eradicate the tumor Two illustrative cases are incorporated in this report The patient in case 41 received fourteen bronchoscopic treatments during a period of seven years without results She ultimately underwent a lobectomy with the removal of a sizeable intrapulmonary tumor (fig 103) The patient in case 42 is still under observation but it is feared that she too will meet the same fate

That some adenomas are confined uniquely to the bronchial lumen has been demonstrated by Jackson, and Case 39 in the present series is illustrative in this respect (fig 104) Such tumors disappear under local treatment

Lobectomy or pneumonectomy is resortec tances when the size
and sessile attachment of the tumor chos al
impossible or when putrid infection
bronchiogenic adenoma tiall
ultimately become ca vis
moment the diagnosis at

ILLUSTRATIVE CASES

Bronchiogenic Adenoma or Pulmonary Tuberculosis

Case 41 History A woman of thirty nine was admitted to the hospital in 1937, complaining of pain at the base of both lungs Her past family and marital histories were noncontributory She had been well until 1933 when she contracted a severe cold accompanied by a stubborn cough During a coughing spell she expectorated about half a glassful of bright red blood and a few days later another hemoptysis occurred amounting to about 2 glassfuls

Roentgenographic examination showed moderate cylindrical dilatation of the bronchi at the bases The sputum was negative for tubercle bacilli She was discharged from the hospital after several weeks with the diagnosis of pulmonary tuberculosis

Although her cough abated expectoration of blood persisted On fluoroscopic examination a shadow at the base of the left lung was noticed Pain in lower chest persisted as well as the sporadic hemoptyses which at times amounted to half a cupful She lost some weight After a profuse hemorrhage she was admitted to the Montefiore Hospital

Bronchoscopy performed in May 1937 disclosed a readily bleeding purplish mass on the posterolateral branch of the bronchus of the lower lobe of the right lung

Roentgenologic examination revealed a pear shaped mass about 5 cm in diameter within the pulmonary parenchyma it was situated on the right side, external to the cardiac shadow A roentgenographic examination performed seven months later following the injection of iodized poppy seed oil showed that the oil penetrated with difficulty into some branch bronchi of the lower lobe in the neighborhood of the mass One branch bronchus in the vicinity was completely obstructed and the lung around it showed no aeration

The diagnosis was adenoma of the bronchus of the lower lobe of the right lung The patient was treated by diathermy coagulation through the bronchoscope

Interval Course She was discharged from the hospital improved but soon small hemoptyses recurred At times blood kept oozing for hours While bronchoscopically the bronchial lumen was virtually patent roentgenologically the tumor within the pulmonary parenchyma showed steady growth From 1937 to 1944 the patient was admitted to the hospital fourteen times receiving treatment through the bronchoscope Hemoptyses could not be controlled In 1944 it was decided to perform a lobectomy

Lobectomy At the operation the pleura overlying the tumor showed no inflammatory changes, the pleural cavity was patent, and most of the lung was crepitant and of normal color A solitary tumor lobulated soft and encapsulated, measuring 4 5 cm was found in the center of the lobe (fig 108) About 0 5 centimeter from the mass the main lobar bronchus showed a defect filled with tumor, which had apparently originated here There was a moderate bronchial dilatation

Microscopic Structure of Tumor The tumor was divided into irregular lobules by broad bands of fibrous tissue (fig 108) It was made up of nests of branching and anastomosing columns of uniform cells separated

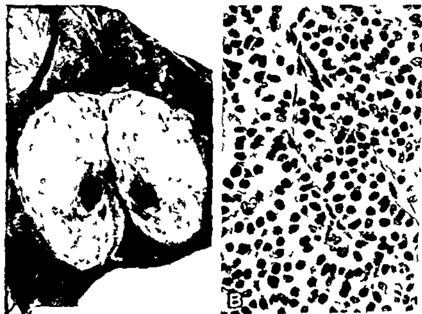


Fig 108 (Case 41) A cut surface of the adenoma removed at operation B microscopic structure of the tumor

in places by connective tissue The cells were polyhedral in the center of the nests and cuboidal or columnar at the periphery The nuclei were round and stained deeply *No mitoses were found* The stroma was vascular, and the blood vessels were often engorged with blood In the vicinity of the growth tumor cells were seen within the wall of a compressed bronchus but no tumor was found elsewhere A comparative study of the histologic nature of the tumor with that of the biopsy specimen removed eight years previously proved them to be identical

Comment The case is characteristic in the onset of the disease with cough and bloody expectoration, and in its protracted course. Although the sputum was invariably negative for tubercle bacilli, the diagnosis of tuberculosis was entertained until the bronchoscopic examination revealed the nature of the disease. As the tumor grew endobronchially and within the pulmonary parenchyma its bronchoscopic removal was not alone sufficient to cure the disease. However, it was of importance in keeping the bronchial lumen patent, thus preventing atelectasis and putrid infection of the lung. About twelve years after the onset of symptoms lobectomy was resorted to, resulting in cure.

The patient was readmitted to the hospital two years later for carcinoma of the breast. It would appear then that, although she had lurking possibilities for carcinogenesis, neither time nor repeated trauma had led to the transformation of the benign adenoma into a malignant carcinoma.

Case 42 History A single women, clerk, aged twenty seven, dated her illness back to February 1940, when she became aware of pain in chest, cough, night sweats and loss of weight and the fact that her sputum was blood streaked on several occasions. The diagnosis of pulmonary tuberculosis was made, she was given rest in bed which led to her improvement until February 1941, when small hemoptyses recurred. The diagnosis of tuberculosis was reaffirmed, and a futile attempt to induce pneumothorax was made. She was again ordered to bed and remained bedridden until September when she was transferred to a sanatorium for tuberculous patients. Her sputum was free from tubercle bacilli. For several months she had perceived a wheezing sound in the chest.

On admission to the Montefiore Hospital she appeared to be well nourished. Loud sonorous rales were heard throughout the chest. The vital capacity was 2600, the sedimentation rate 40.

Roentgenologic examination revealed a wedge-shaped shadow with its base at the mediastinum; it extended from the right hilus toward the periphery, at the level of the third rib anteriorly. There was some shrinkage of the upper lobe of the right lung, the trachea was retracted to the right side and the right lung showed reduced expansion. The homolateral leaf of the diaphragm was elevated (fig 100). The findings were indicative of lobar atelectasis due to stenosis of the right bronchus of the upper lobe. The impression was that one was dealing with a moderately advanced pulmonary tuberculosis accompanied with tuberculous endobronchitis.

Bronchoscopy On bronchoscopic examination the right bronchus was occluded by a smooth mass which had apparently originated in the posterior wall of the upper lobe of the right lung. A biopsy specimen on

histological examination showed the tumor to be an exact replica of that in case 41

Comment While in case 41 the disease had been observed in the pre obstructive phase in this case obstruction was quasicomplete when the patient came under observation She had as yet escaped the sequel of bronchostenosis such as putrid infection of the lung or empyema She is being treated bronchoscopically, but it is feared that eventually a lobectomy or pneumonectomy will have to be resorted to Unlike the patient in



FIG 109 (Case 43) Roentgenogram of the lungs showing a triangular shadow on the right due to atelectasis caused by obstruction of the bronchus

case 41 in which the diagnosis of tuberculosis was entertained for a short time only this patient was treated for tuberculosis for nearly two years

ADENOMA OR CARCINOMA

Case 43 *History* A pharmacist of sixty five years was seen for the first time in June 1944 for pain in the dorsal part of the spine His past history was irrelevant and the physical examination revealed no findings worthy of note On roentgenologic examination the spine showed no abnormalities but a well circumscribed mass measuring about 6 cm in diameter was noticed in the upper lobe of the right lung (fig 110) The diagnosis of bronchiogenic carcinoma was made and the patient subjected to radiation therapy While under treatment a pulmonary infection developed to which he succumbed

At necropsy the lungs showed bronchopneumonia The apices were adherent to the chest wall In the upper lobe of the right lung posteriorly a firm tumor about 5 cm in diameter was found It surrounded a secondary branch of the bronchus of the upper lobe without however narrowing the bronchial lumen The bronchial wall was normal for about 3 cm, after which it abruptly closed the bronchus being buried within



Fig 110 (Case 43) Roentgenogram showing bronchiogenic adenoma in the upper lobe of the right lung

the mass which enveloped it The lungs showed considerable fibrosis The tracheo bronchial lymph nodes contained no tumor

On microscopic examination the tumor was partitioned into lobules resembling those of the pancreas or the salivary gland The cells were wholly degenerated but their structure could be identified as polygonal or roughly round with round nuclei The new growth was surrounded by a capsule the outer coat of which showed lamellary hyalinization while the inner coat was densely hyalinized Beyond the hyalin there was a ring of young fibrous tissue

Comment In this case the diagnosis of bronchiogenic carcinoma was made erroneously on roentgenologic evidence only In the past the tumor was often mistakenly identified by pathologists as polypoid carcinoma or carcinoid Clinicians diagnosed the disease in the early stages as tuberculosis later interest was centered on the pulmonary complications, such as bronchiectasis abscess or empyema and the adenoma was overlooked Unlike carcinoma adenoma is often the cause of extensive dilatation of the bronchi This is due to complete occlusion of the lumen of a large bronchus and to the protracted course of the disease

In this case the tumor which had originated in the mucosa of a smaller bronchiole (peripheral adenoma) had caused disturbances which were apparently so mild as to be disregarded by the patient He received 7 000 r delivered to his chest Whether the degeneration of the tumor was due to treatment with the x rays or to other causes could not be ascertained

ADENOMA WITH BONE AND CALCIUM FORMATION

Case 44 *History* A woman of 62 noticed blood streaked sputum and occasionally hemoptysis which had persisted for a few years Examination six years later revealed a picture diagnosed bronchiogenic carcinoma Reexamination two years later showed the shadow unchanged and as it moved with respiration it was interpreted as a benign tumor or possibly an organized abscess of the lung Two years later she died of a cardiac condition

At necropsy the lower lobe of the right lung was shrunken and distorted and the pleura along the inferior border was thickened and deeply retracted A firm mass was felt posteriorly in the region of the lower and middle lobes (fig 111) and the rest of the lung was noncrepitant The mass (3 5 by 4 5 cm) was lodged in the lower portion of the lung posteromedially It arose from the main bronchus to the lower lobe about 3 cm from the carina completely obliterating the bronchial lumen The branches of the lower lobe were almost completely obliterated and replaced by tumor Only fragments of cartilage remained in the bronchial wall in this region

The newgrowth grew within the bronchial lumen and within the parenchyma of the lung It was sharply demarcated encapsulated and hard as stone On cut surface it showed bone and dense fibrous and hyalinized tissue The larger bronchial branches and the blood vessels in the vicinity of the tumor were merely pushed aside and compressed but not eroded or occluded The bronchus to the middle lobe was compressed but not obliterated and the lobe was partially atelectatic No metastases were present

On microscopic examination (fig 111 B and C) the tumor was made up

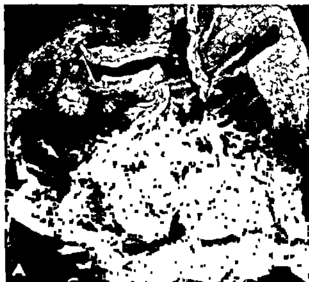




FIG 111 (Case 44) A cut surface of the adenoma surrounded by a capsule B microscopic structure of the tumor, C showing myelopiesis (upper segment of photograph) and bone formation

of small polygonal cells showing no mitoses Areas of degeneration, of fibrosis and hyalinization were scattered throughout the sections Bone formation and nests of myelopoiesis were seen here and there

Comment This benign tumor took origin in the wall of a large bronchus which it obliterated Within the lung it formed a sizeable mass which compressed adjacent structures *but did not invade them* It grew slowly and became extensively ossified and hyalinized There were foci of extramedullary myelopoiesis

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Supplement III

BRONCHIOGENIC MESODERMAL TUMORS

Tumors arising from mesodermal elements of the bronchial wall are rarely encountered Some of them have a tendency to grow intrabronchially imitating ectodermal (epithelial) carcinoma

Chondroma This tumor is made up of cartilage Most observers believe that it originates in aberrant bronchial cartilage or that it is an embryonal rest It is usually encapsulated, round or oval, nodular or lobulated, becoming in time calcified and ossified It is located near the surface of the lung or between the lobes

In most instances the tumor was discovered accidentally In some the symptoms consisted of cough, asthmatic attacks and occasionally, hemoptysis In Paul's case a man of 69 had suffered from asthma since adolescence A polypoid chondroma causing bronchostenosis, shrinkage of the lung, bronchiectasis and empyema was found at autopsy

Before the advent of the x rays the tumor remained undiagnosed during life With the x rays it is seen as a round, sharply delineated mass of great density, surrounded by normal pulmonary tissue The picture is not unlike that found in hydatidiform disease

Leiomyoma This tumor originates in the smooth muscle of the bronchial wall In a case reported by Neuman, it concerned a woman of 60 who showed a malignant tumor with multiple metastases The diagnosis of leiomyoma was made after the patient's death

In Kramer's case a girl of 15 complained of cough and blood streaked sputum Roentgen rays of the chest showed a lesion compatible with bronchial obstruction, and bronchoscopic examination revealed occlusion of the lumen of the bronchus to the right lower lobe Removed tissue showed myoblastoma The patient was treated bronchoscopically and was apparently cured

Brahdy reported a case of a fibroleiomyoma in a girl of 18 The tumor was discovered accidentally during a roentgenologic examination of the chest The film showed a round area of density at the base of the right lung, which bronchoscopically appeared to be behind the dome of the diaphragm, it moved synchronously with the diaphragm and was within the lung The diagnosis of tuberculoma was made and the tumor excised The true nature of the growth was discovered under the microscope

Randal and Blades reported a case of a leiomyosarcoma in a Negro man, 34 years old who complained of cough, dyspnea and weakness Hemopty

sis occurred about a year after the onset of symptoms. When hospitalized he showed a leucocytosis and a sedimentation rate of 28 mm in one hour. On roentgenologic examination there was an area of density in the right hilus, the right leaf of the diaphragm was elevated and the heart and the mediastinal structures were shifted to the right side. Bronchoscopy revealed a smooth, round tumor protruding into the lumen of the bronchus to the right upper lobe, occluding the main bronchus and partially covering the carina. The diagnosis of bronchiogenic carcinoma was made but histologically it was found to be a leiomyosarcoma. The patient died during an attempt to perform a pneumonectomy. The tumor was irregularly circumscribed and for the most part encapsulated. It measured 10 to 14 cm in diameter, was very cellular and locally infiltrating. Neoplastic cells were found in the alveolar spaces. Only seven cases of this type have been found in the literature.

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MEDIASTINAL TUMORS

Chapter XII

TUMORS OF THE MEDIASTINUM

NEUROGENIC

The thoracic cage is the seat of pulmonary as well as extrapulmonary tumors. The latter may be primary, secondary, benign or malignant. The benign may be solid (neurogenic tumors, fibromas, chondromas, lipomas) or cystic (dermoid cysts, bronchiogenic cysts). The malignant tumors include teratomas, thymomas, lymphomas and carcinomas (of thymic or thyroid origin).

Anatomically the mediastinal space may be divided into three compartments: anterior, middle and posterior. Carcinoma and adenoma are essentially mid mediastinal tumors; terato-dermoids, anterior mediastinal; and neurogenic tumors, posterior mediastinal.

These tumors, once regarded as a rarity, are at present found with relative frequency. Their identification in recent years is attributed to the wide spread use of roentgen rays. Their number will doubtless increase with the practice of mass roentgenography embracing individuals of all age periods. Routine roentgenographic examination of the chest has led to detection of 94 of 109 cases of mediastinal tumors at Army Thoracic Centers in the United States.

Neurogenic tumors are of interest per se as well as from the point of view of the differential diagnosis with other tumors of the chest. Contrary to the prevailing opinion, many of them are malignant at the start; others become malignant in the course of their progress. In a series of 18 cases reported by Kent and Blades 7 were malignant. Of 105 cases collected by them from the literature 39 cases or 37 per cent were malignant. Mediastinal tumors of neurogenic origin and terato-dermoids are the most important from the clinical point of view and will be dealt with in greater detail. Others (bronchiogenic cysts, lipomas) will be considered briefly.

Embryologic and Anatomic Data. In the early stages of embryonic life cellular elements known as neuroblasts separate from the ganglionic crest of the medullary tube, wander away and form sympathetic ganglia (nerve plexuses) and also the medulla of the suprarenal glands. The primitive neuroblasts divide and produce a new generation of cells, neurocytes or sympathogonia. The latter serve as a point of departure for three systems (fig. 112).

1 The sympathetic system in which they differentiate into sympathoblasts and ganglion cells

2 The chromaffin system in which they differentiate into pheochromoblasts and pheochromocytes

3 The supporting system in which they differentiate into glial astroblasts and astrocytes

The peripheral nerves are made up (a) of neurons (neuraxons, axis cylinders), bundles of which are enclosed in a membrane, epineurium (b) of a perineurium which envelops individual nerve fibers and (c) of a

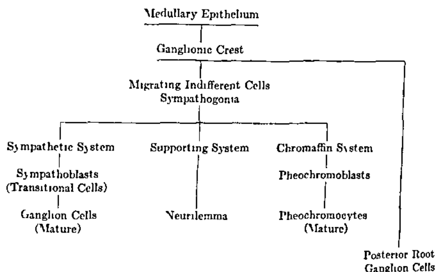


FIG 112 Schematic presentation of the embryologic development of the sympathetic nervous system

membrane insulating the nerves from the surrounding tissue, the sheath of Schwann

Histogenesis Since nerves are ubiquitous neurogenic tumors are apt to occur in every part of the body They may arise from the sympathetic peripheral or supporting systems be malignant or benign depending on the stage of differentiation of the mother cell from which they arose A classification of tumors of the sympathetic system as proposed by Bielschowsky is presented in Fig 113 The most malignant tumors sympathogoniomas originate from the primitive sympathogonia The less malignant sympathoblastomas originate from sympathoblasts Finally, the benign ganglioneuromas originate from fully differentiated mature ganglion cells Of the tumors of the chromaffin system the pheochromoblastomas are malignant while the pheochromocytomas are benign

Tumors which originate from peripheral nerves arise not from neurons (axis cylinders) but from the membrane surrounding them. Pathologists are still uncertain as to the particular perineural structure which is the source of the tumors. According to one school of observers neurogenic tumors arise from the specific investment which separates and insulates nerve tissue from the surrounding elements, the cells making up the syncytium of Schwann. The tumors were therefore designated as Schwannomas (neurinomas, neurocytomas). Masson, an exponent of this theory wrote:

"The specific cells of the tumor are connected in a syncytium like Schwann cells; they possess elongated nuclei and they are grouped in networks, in branches and in palisades. The latter structures are pathognomonic. The palisades consist of oval nuclei aligned in the same transverse plane like staves on a barrel. On each side of this nuclear palisade or on one side only there is a fibrillar band parallel to it. The fibrils are oriented like the nuclei, running perpendicular to the nuclear band. Thus a palisade system is formed by two nuclear palisades parallel to each other and an intervening fibrillar palisade."

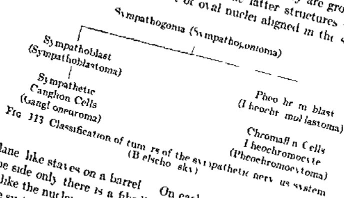


FIG 113 Classification of tumors of the sympathetic nervous system (Bielschowsky)

Penfield maintained that the tumor originates not from the Schwann cells but from the endoneural or perineural connective tissue which invests the nerves. He wrote:

"Because of varying intermixtures of nerve fibers with connective tissue the term neurofibroma is descriptive in the sense that it is a fibroma in and on a nerve, the fibers of which contribute toward the formation of the tumor. Neurofibroma—a tumor with both nerve fibers and connective tissue . . . is not a new growth of nervous tissue although there are nerve fibers and apparently nerve collaterals running in it. It is not a simple fibroma but a fibrous connective tissue reaction that is part of a more general process. . . . The perineural fibroblastoma must be considered to

arise from the perineural or endoneural connective tissue which invests nerve fasciculi and fibers

Tumors of neurogenic origin found in the thorax are ganglioneuromas and neurinomas (neurofibromas)

Ganglioneuroma

Ganglioneuroma (believed by some observers to be a developmental anomaly) is a slow growing solitary round or oval tumor invested in a capsule It is moderately soft and pale gray Histologically it is composed of small round or elongated embryonal nerve cells embedded in a delicate reticulum also of scattered multipolar ganglion cells In case the tumor contains a preponderance of fibrous tissue it is defined as ganglioneurofibroma

Ganglioneuroma arises in intimate connection with one of the sympathetic ganglions On rare occasions it takes origin in the vicinity of or within a vertebral foramen where it may grow both into the spinal canal and into the thoracic cavity assuming the form of a dumbbell or an hour glass (fig 114) In the thorax ganglioneuroma extends from the bodies of the vertebrae forward and away from the midline pushing the parietal pleura in front of it It does not invade the lung but may erode the bone

Neurinoma (Schwannoma)

Neurinoma originates in the roots of the thoracic spinal nerves or in the intercostal nerves forming a nodular swelling composed of spindle shape cells arranged in a palisade order or in whorls Microscopically the solitary neurinoma is a replica of the individual neuromatous swelling found in multiple neurofibromatosis or v Recklinghausen s disease The latter is a systemic and not a neoplastic disease However cases have been observed where a large solitary tumor was present in the mediastinum in individuals with multiple neurofibromatosis

Usually benign neurinomas undergo in rare instances a malignant (sarcomatous) transformation

Diagnosis

Localization Intrathoracic neurogenic tumors are as a rule located in the upper posterior mediastinum In 18 proved and 3 presumptive cases studied by Kent and Blades 19 were in the posterior mediastinal space In 101 cases from the literature only 2 were found in the anterior mediastinum The authors emphasized that in any case of a tumor found in the posterior mediastinal space the presumption is strong that it is neurogenic in nature

Age and Sex The tumors are encountered in all age groups Recent literature abounds in reports of ganglioneuromas found in children It

would appear that when found in older individuals it is more liable to be malignant

Both sexes are about equally affected

Symptoms Unlike the intrapulmonary tumors the extrapulmonary neurogenic manifest themselves mildly as a rule Following a protracted asymptomatic period patients begin to complain of indefinite pains and aches or of tightness and fullness in the chest Occasionally the pain is radicular In most cases as in the illustrative herein presented the new growth was discovered by accident on a routine roentgenologic examination of the chest Generally symptoms depend on the size and the location of the tumor

Stout observed a case in which a ganglioneuroma of the upper cervical ganglion reached the area of the tonsil pushed aside the tongue and extended up to the submaxillary fossa behind the mandible In the neck the tumor is usually located between the carotid artery and the jugular vein in front of the vagus nerve When the upper cervical ganglion is involved it induces the syndrome characteristic of apical bronchiogenic carcinoma Dolley and Brewer removed a ganglioneuroma following a preoperative diagnosis of a carcinoma with bronchostenosis

Frost and Wolpaw reported a case of a sympathoblastoma producing the symptomatology of a superior pulmonary sulcus tumor Riggs and Good observed a patient in whom compression and obstruction of the trachea was caused by a contiguous ganglioneuroma

Pressure on the trachea causes cough dyspnea cyanosis stridor and hoarseness Partial occlusion due to pressure on the superior ven induces edema of the upper part of the body cyanosis of face and dila of the superficial veins (vena caval syndrome) Pressure on bronchi feres with aeration and produces lobar or lobular atelecta is followe pneumonitis In a case of benign ganglioneuroma removed by Harrin a hemorrhagic pleurisy was found The opinion is prevalent that prin nerve tumors are dangerous

Of interest are tumors arising in an intervertebral foramen They u ally grow in two directions toward the mediastinum and toward the spi canal so-called hour glass tumors mentioned above (fig 114) In the cases the early symptoms refer to pressure on the cord while the intrath racic remains silent and is discovered by accident It is conceded tha when clinical manifestations are definite the possibility of a malignan metamorphosis should be considered

Roentgenologic Examination

If the clinical symptomatology is vague and not pathognomonic the roentgenologic picture is characteristic The tumor is visualized as a well

defined round or oval mass lying in the posterior mediastinal space in the paravertebral gutter Lateral and oblique films and fluoroscopy help to determine the position of the growth But particularly demonstrative is the picture following the induction of artificial pneumothorax (fig 117) which outlines the extrapulmonary localization of the growth In the differential diagnosis aneurism of the descending portion of the aorta, so-called diving goitre lymphoblastoma and Hodgkin s disease are to be ruled out Aneurism is a pulsating structure goitre moves in the process of swallowing lymphoblastoma and Hodgkin's disease are radio sensitive while neurogenic tumors are radio-resistant

Angiographic visualization of the heart and great vessels by intravenous injection of radiopaque compounds is an important procedure in the diag

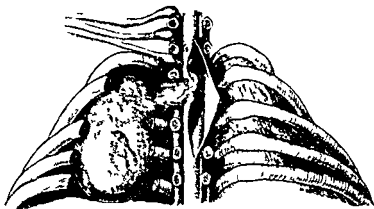


FIG 114 Neurogenic hour glass tumor (neurinoma) of the mediastinum (Heuer G S So called hour glass tumors of the spine Arch Surg 18 935 1929)

nosis of mediastinal tumors particularly in the differential diagnosis between vascular (aneurism) and neoplastic lesions Most observers are of the opinion that in a large number of cases aneurisms of the aorta do not pulsate while mediastinal tumors show pulsation through impact with a large vessel An aneurism usually fills with diodrast except when it is clotted or when there is a small neck

Treatment

Since these tumors are radio resistant surgery is the treatment of choice

Illustrative Cases

Case 45 History A young man of 18 had enjoyed good health until 1943 when he was rejected from the Army because of an abnormality found in his chest

Examination on admission to the hospital revealed a well developed and

nourished man The entire right thorax was tympanitic and the breath sounds considerably diminished over the right apex anteriorly and the right base posteriorly There was diminution of tactile fremitus and vocal resonance throughout the whole lung

Roentgenologic Examination The apex of the right lung showed a sharply circumscribed area of density the lower border of which was convex (fig 115) A right anterior oblique view and fluoroscopy revealed a mass occupying the posterior portion of the pulmonary apex Examination following the induction of a pneumothorax revealed it outside the lung There was a

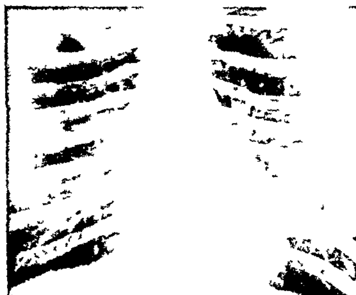


FIG 115 (Case 45) *Ganglioneuroma of the right apex*

slight displacement of the heart and mediastinal structures toward the left The diagnosis was neurogenic tumor at the apex of the right lung

Operation When the pleural cavity was exposed the tumor was seen as an ovoid mass with its larger pole at the outer extremity and the smaller end lying against the lateral surface of the vertebral bodies It was situated in the vertebral gutter lying transversely in front of the second and third ribs reaching down to the upper border of the fourth rib It was covered by the posterior parietal pleura The apex of the upper lobe showed a convex depression corresponding with the inferior surface of the neoplasm and equal in size to it

Pathological Description The removed tumor was roughly egg shaped

and encapsulated, measuring 5 5 by 3 6 by 3 8 cm It was rubbery in consistency and covered with a smooth capsule 0 5 cm in thickness easily stripped from the tumor leaving a slightly grooved surface On cut surface the tissue was translucent and pale-brown in color On microscopic examination it was found to be a ganglioneuroma

Comment The pulmonary apex is the seat of choice of neurogenic and allied tumors Ray and Frost and Wolpaw reported cases of apical sympathoblastomas I observed a patient with a pheochromocytoma situated at the apex of the left lung The patient showed Horner s syndrome and ipsilateral anhydrosis The tumor about 6 cm in diameter was found to lie above the lung which it compressed but had not invaded It did not impinge on the brachial plexus (The patient entered the hospital for hypertention and hemiplegia and died of congestive heart failure)

Case 46 History A plumber twenty one years old who suffered from *pain under the right shoulder blade for four years was admitted to the hospital* The pain appeared on exertion on abrupt motion and after prolonged use of muscles of the upper back It was relieved by lying on the right side and by resting the arm in a certain position He disregarded the disease until a roentgenologic examination for induction into the Army revealed a tumor in his chest

Physical examination on admission showed him to be well developed and nourished His cardiac vascular and respiratory systems were normal His blood and body fluids failed to show abnormalities

Roentgenologic examination revealed a rounded mass of homogeneous density about 9 cm in diameter lying lateral to the second third fourth and fifth dorsal vertebral bodies and occupying the upper medial and posterior portions of the right chest (fig 116) After the induction of a pneumothorax the mass appeared to be free from any connection with the lung It occupied the paravertebral sulcus on the right and on lateral and oblique films was seen to be broadly adherent to the vertebral column at the level of the fourth fifth and upper half of the sixth thoracic vertebrae (fig 117) The lungs showed no disease

Operation At the operation an elliptical mass was found in the right vertebral gutter extending from the fourth to the seventh ribs mesially it was close to the vertebral bodies It protruded forward *into the pleural cavity* for about 6 cm being densely adherent in part to the fourth and fifth ribs upon which it rested giving the impression of infiltrating them It was judged that the growth was malignant and it was removed with the ribs

Pathological Report The specimen consisted of an encapsulated roughly oval mass measuring 6 8 by 7 by 3 5 cm It was grayish white smooth



Fig 116 (Case 46) A ganglioneuroma of the superior thoracic ganglion B cut surface of the tumor removed surgically

and encapsulated measuring 5 5 by 3 6 by 3 8 cm It was rubbery in consistency and covered with a smooth capsule 0 5 cm in thickness easily stripped from the tumor leaving a slightly grooved surface On cut surface the tissue was translucent and pale brown in color On microscopic examination it was found to be a ganglioneuroma

Comment The pulmonary apex is the seat of choice of neurogenic and allied tumors Ray and Frost and Wolpaw *reported cases of apical sympathoblastomas* I observed a patient with a pheochromocytoma situated at the apex of the left lung The patient showed Horner s syndrome and ipsilateral anhydrosis The tumor about 6 cm in diameter was found to lie above the lung which it compressed but had not invaded It did not impinge on the brachial plexus (The patient entered the hospital for hypertension and hemiplegia and died of congestive heart failure)

Case 46 History A plumber twenty one years old who suffered from pain under the right shoulder blade for four years was admitted to the hospital The pain appeared on exertion on abrupt motion and after prolonged use of muscles of the upper back It was relieved by lying on the right side and by resting the arm in a certain position He disregarded the disease until a roentgenologic examination for induction into the Army revealed a tumor in his chest

Physical examination on admission showed him to be well developed and nourished His cardiac vascular and respiratory systems were normal His blood and body fluids failed to show abnormalities

Roentgenologic examination revealed a rounded mass of homogeneous density about 9 cm in diameter lying lateral to the second third fourth and *fifth dorsal vertebral bodies and occupying the upper medial* and posterior portions of the right chest (fig 116) After the induction of a pneumothorax the mass appeared to be free from any connection with the lung It occupied the paravertebral sulcus on the right and on lateral and oblique films was seen to be broadly adherent to the vertebral column at the level of the fourth fifth and upper half of the sixth thoracic vertebrae (fig 117) The lungs showed no disease

Operation At the operation an elliptical mass was found in the right vertebral gutter extending from the fourth to the seventh ribs mesially it was close to the vertebral bodies It protruded forward into the pleural cavity for about 6 cm being densely *adherent in part* to the fourth and fifth ribs upon which it rested giving the impression of infiltrating them It was judged that the growth was malignant and it was removed with the ribs

Pathological Report The specimen consisted of an encapsulated roughly oval mass measuring 6 8 by 7 by 3 5 cm It was grayish white smooth

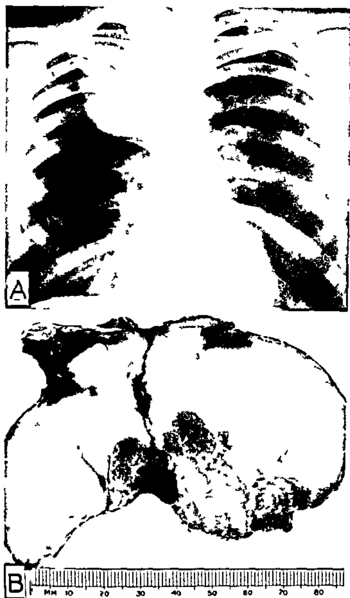


Fig. 116 (Case 46.) A ganglioneuroma of the superior thoracic ganglion B cut surface of the tumor removed surgically

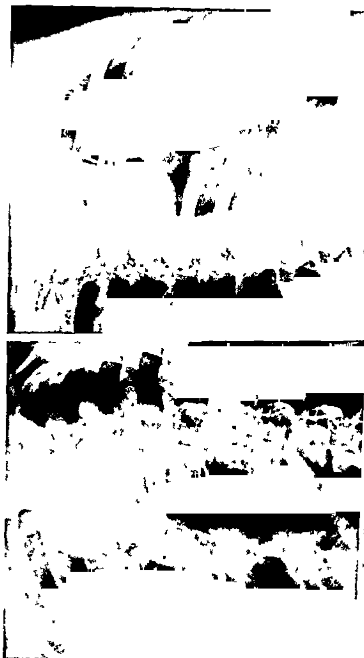


Fig 117 (Case 46) Right and left oblique views after the induction of pneumothorax

elastic and surrounded by a paper thin capsule On cut surface it was shiny and translucent and had a somewhat mottled appearance Pieces of two ribs were attached to the growth one lying on the surface the other buried in tumor The latter was densely adherent to the periosteum of the rib from which it was separated with difficulty (fig 116) In the region of the neck of the ribs the tumor had grown between the two ribs and expanded on the opposite side into an irregular lobulated encapsulated mass measuring 4 by 2 5 by 2 cm The microscopic diagnosis was Ganglioneuroma with invasion of ribs

Case 47 *History* A man thirty years old was admitted to the hospital with the diagnosis of tumor of the lung The growth had been discovered 10 years previously on routine examination of the chest (fig 118 A) Periodic examinations showed that it had been steadily increasing in size without however, producing symptoms In 1943 the patient was rejected for military service because of the intrathoracic growth

Examination revealed a well nourished individual in no distress The chest showed dullness and diminished breath sounds in the lower lobe of the left lung posteriorly No abnormalities were disclosed elsewhere

Roentgenologic examination of the thorax disclosed an area of increased density, oval in shape measuring 12 cm in length 9 5 cm in width and 12 cm in depth It was situated in the medial portion of the right posterior mediastinum in the paravertebral region (fig 118 B) The heart was displaced to the left A pneumothorax was induced and showed the tumor to be extrapulmonary The diagnosis was Neurinoma (Neurofibroma) of the medial portion of the right mediastinum

TERATO DERMOIDS

Definition Dermoid cyst is a cystic structure with a thick wall made up of dense connective tissue lined by stratified squamous epithelium The cyst is filled with a translucent or gelatinous fluid

Unlike the dermoid cyst teratoma is a solid structure containing cystic areas Formerly the two were sharply demarcated the dermoid cyst was believed to be composed of tissue derived from one embryonic layer the ectoderm while the teratoma was said to be made up of tissues derived from the three germinal layers ectoderm mesoderm and entoderm At present a clean cut separation is not considered tenable because the dermoid cyst like the teratoma often harbors elements from all germinal leaflets The name of terato-dermoid suggested by Rusby for this group is considered preferable

Location The terato-dermoid is located in the anterior mediastinum behind the sternum encroaching upon one side of the thoracic cavity Occa



Fig 118 (Case 47) A neurinoma in the right mediastinum found in 1937, B seven years later showing marked increase in size of the tumor

sionally it protrudes into the suprasternal fossa and the region of the neck. On roentgenologic examination it is circumscribed with well defined sharp edges and usually attached to the surrounding structures the large vessels and pericardium, from which it can be detached with difficulty. The pulsation which it produces is due to the impact from the heart and large vessels.

Clinical Manifestations Although the terato dermoids are embryonic anomalies they do not manifest themselves until adolescence or early adult life. Of 174 patients analyzed by Rusby 68 showed symptoms between the ages of 20 and 29, 62 between the ages of 29 and 59 and 44 below the age of 20. They apparently remain dormant until the advent of infection or malignant transformation. The latter occurs more often in the solid teratoma. According to Rusby's figures the dermoid cyst becomes malignant two and one half times less often than the solid teratoma. Blades related a case of a patient admitted to the hospital for hemoptysis, dyspnea and swelling of the cervical veins. At operation a teratoma was found to invade the middle lobe of the right lung. Lappily in a series of 245 cases found 28 or 11.4 per cent malignant. Heuer and Andrus found malignant changes in 5 of 13 cases and Blades in 6 of 20.

Trauma, cancerous transformation and also infection stimulate growth of the "monstrosity" which causes pressure on the adjacent organs or structures.

Cough Cough, particularly marked when the patient is in a recumbent position, is present in almost all cases. It is dry often wheezing productive of a characteristic gelatinous expectoration sometimes containing hair. The gross inspection of the sputum is of utmost importance for it early provides suggestive data. The sputum is often blood streaked occasional hemoptysis occurs. When the tumor is predominantly on the left side it is apt to cause hoarseness at an early date.

Dyspnea In the early stages dyspnea is exertional only but with the advance of the disease and increase in size of the growth shortness of breath is a constant feature sometimes it is asthmatic in nature.

Bronchostenosis, Broncho-Pleural Fistula As in carcinoma or adenoma the condition of the adjacent bronchus is of utmost importance. The pressure caused by the terato-dermoid leads to compression of the bronchus and to narrowing of the lumen (extrinsic stenosis) at times completely occluding it. The segment of the lung distal to the obstruction becomes infected resulting in pneumonitis, abscess formation and bronchiectasis. As in adenoma, attention was drawn to the complications while the primary disease was overlooked.

Not only the lung or the cyst, but the pleural cavity as well becomes infected by way of a broncho pleural fistula. Indeed, empyema is not a rare complication of the neglected terato-dermoid. Empyema also follows a spontaneous rupture of the cyst into the pleural cavity.

Pain Pain in chest is a constant phenomenon, caused by a pleuro-pneumonitis When the growth encroaches on the brachial plexus it induces symptoms imitating apical bronchiogenic cancer Pain in the shoulder radiates down the arm along the ulnar side, there occur numbness and tingling in the hand and fingers, muscular weakness, paresis and Horner's syndrome

Diagnosis It is very important to arrive at a diagnosis before infection has set in For infection promotes the growth with ensuing complications including possible transformation into malignancy

The sputum is very often the first sign to attract attention it is gelatinous and not infrequently contains hair With the advance of the disease pressure upon adjacent structures pulsations of the veins of the neck and sometimes swelling of the neck make their appearance

Signs or symptoms of intrathoracic pressure in early adult life should always prompt a search for a terato-dermoid

The area occupied by the tumor is flat to percussion with absence of breath sounds and the entire hemithorax may show restriction of respiratory excursions Inspection may reveal bulging of the thorax in the region of the growth

Roentgenologic examination shows the position of the growth in the anterior mediastinum and its relation to the lungs and other mediastinal structures The presence of teeth clinches the diagnosis

Differential Diagnosis Thymoma and lymphosarcoma are found in the same position and are differentiated, among other things by a therapeutic test with radiation to which they are sensitive while the terato-dermoid is radio resistant Myasthenia gravis often accompanies thymoma Bronchiogenic cysts lipomas of the mediastinum and aneurism of the aorta should be included in the differential diagnosis

The mediastinal type of bronchiogenic carcinoma by its topography and symptoms resembles ter ... lmon
ary and intrabronchial
cancer and gelatinous

LIPOMA

Whether mediastinal lipomas are always congenital has not been established In the congenital cases the lung was found hypoplastic The tumor has rarely been observed Only 36 cases have been collected by Blades from 1782 to 1941 Like other mediastinal tumors an increase in incidence has been noted in recent years, most likely as a result of an increase interest in intrathoracic neoplasms

Lipomas originate from adipose tissue of the mediastinum subpleural fat or from fatty tissue of the bronchial wall Most of them occurred in males

whose age varied from 1 to 57 years Their size oscillated between that of the head of a newborn infant to that of an orange Of 11 cases collected by Yater and Lyddane the largest weighed 17 lbs 6 oz, the smallest twice the size of a hen's egg' In Walton's case the tumor measured 30 by 23 by 22 cm and weighed 16 8 lbs Like the terato-dermoids they are situated in the anterior mediastinum

Lipomas are divided into two groups 1, confined in toto to the thoracic cavity, 2, partially extrathoracic The latter variety is formed by the penetration of the intrathoracic tumor through an intercostal space or through a defect in the sternum, forming a bulge under the skin and muscles of the chest wall The intrathoracic lipomas make their way into one or both pleural cavities, while those originating in the upper mediastinal space are apt to grow upward into the neck

Clinical Manifestations Symptoms depend on the size and the location of the tumor Small tumors are usually asymptomatic In the larger ones the symptoms are caused by pressure on the neighboring structures In most cases dyspnea pain in chest and cough were the chief complaints In some edema of the upper extremities was present and in one case dysphagia and epigastric pain was recorded

In Walton's case a woman forty years old had always been below average weight tired easily and suffered from a moderate exertional dyspnea During the last year dyspnea and fatigue increased and retrosternal and epigastric pain appeared For the last three months she complained of nausea and vomiting and developed dysphagia

In Graham and Wiese's case a man of 43 was admitted to the hospital because of a small mass at the base of the neck on the right noticed 6 months previously, of intermittent choking spells and dyspnea He was hoarse dyspneic and cyanotic A lipoma was found in the anterior mediastinum In a review of the histories of 34 patients with intrathoracic lipomas McCorkle found that in 16 instances the patients complained of dyspnea, in 11 of pain in the chest, in 7 of cough, in 2 of hemoptysis and in 2 of hoarseness Eight patients were cyanotic, 3 had edema of extremities and 1 suffered from anginal pains

The varied symptoms of intrathoracic lipomas characteristic of other mediastinal tumors makes the intra vitam diagnosis of the tumor difficult In appearance lipoma resembles a terato-dermoid However, on insertion of a needle in the teratoma one meets resistance, while in the lipoma the needle enters with ease Again, in the terato dermoid gelatinous matter can be obtained while in the lipomas no characteristic contents are obtainable

Radiograms reveal a somewhat lobulated tumor, usually less regularly ovoid than the terato dermoid

Thoracotomy is the diagnostic method of choice

The causes of death in the non operated patients were suppuration of the anterior mediastinum broncho pneumonia pleuritis empyema asphyxia

Differential Diagnosis Terato-dermoids and thymomas situated in the anterior mediastinum are differentiated from a lipoma by an exploratory puncture already mentioned The sputum in the former very often contains hair or gelatinous matter Heuer and Andrus made a diagnosis of a *mediastinal lipoma on the* roentgenograms which were less opaque at the periphery This suggested to them that the tumor was composed of fat because it was more readily penetrable than the compact tissue of other tumors of the mediastinum *Thymomas are as a rule located in the sub-*sternal region On roentgenologic examination the tumor is seen in frontal projection and much less clearly laterally It usually preserves the shape of the normal thymus

Treatment Surgical extirpation of the tumor is the sole therapeutic method

MEDIASTINAL CYSTS (BRONCHIOGENIC ENTERIC GASTRIC)

Of the various cysts found in the mediastinum the gastroenterogenous and bronchiogenic are of interest They are oval or round structures made up of a thick connective tissue wall lined by a mucosa resembling that of the stomach small intestine or the bronchus, respectively The wall of the bronchiogenic cyst reproduces the structure of the bronchus containing *smooth muscle mucous glands and cartilage*

Ordinarily they are solitary multiloculated or trabeculated but occasionally they appear multicystic composed of 2 or 3 cysts The cysts contain mucous or gelatinous material and vary in size from 6 to 10 cm in diameter

In most instances they were confined to the region of the hilus firmly attached to a lobar bronchus In many cases they were found in close proximity to the bifurcation of the trachea attached to the carina or a large bronchus In some cases they were attached to the lateral wall of the trachea the esophagus or within the esophageal wall bulging into the lumen *They have even been found between the trachea and the bronchus* attached to the latter

Once considered a rare finding bronchiogenic cysts like intrapulmonary

cases of the chest They are congenital m[illegible] abnormal budding of the tracheo bronchial tree (pinching off of a bud or diverticulum of the embryonic foregut)

There seem to be no agreement as to whether the cyst normally commu

... usually be demonstrated ... to Lapply "typically the cyst does not communicate with the trachea or the bronchi"

Clinical Manifestations As in other solid or cystic mediastinal tumors the symptomatology depends on the size and location of the growth Small cysts may remain silent for life Symptoms appear when the cyst begins to press on the neighboring organs or structures such as the bronchus or trachea inducing cough Many patients complain of a sense of constriction in the chest Infection of the cyst with pathogens through a bronchial connection leads to increase in its contents which becomes fetid

Auscultation yields a flat note confined to the region occupied by the cyst with abolition of breath sounds However physical examination is of doubtful assistance in the diagnosis for the signs are not pathognomonic

Roentgenologic examination reveals the position of the cyst in the posterior mediastinum, in the vicinity of the ...

by t

the

Treatment The cyst is removed by surgical means

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